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BASICS OF SPIROMETRY

Lung volumes & lung capacities: 00:02:28

1.Tidal volume (TV)
- Amount of air going in & out of the lung during normal respiration

2.Inspiratory reserve volume (IRV)
- It is the excess amount of air over & above the T.V that can be taken inside lungs after forceful inspiration

3.Expiratory reserve volume (ERV)
- It is the excess amount of air above tidal volume which can be expired out of lungs with forceful expiration

4.Residual volume (R.V)
- Amount of air that remains in the lungs even after a forceful expiration

I. Inspiratory capacity (IC)
- It is the maximum amount at that can be breathed in after a forceful inspiration it is always a combination of T.V & IRV

II. Functional residual capacity (FRC)
- It is the amount of the air that remains in the lungs after a normal expiration it is sum total OF ERV & RV

III. Vital capacity [V.C]
- It is the amount of air that can be forcefully expired after a maximal inspiration. It is the sum total of IRV, T.V, ERV

IV. Total lung capacity [TLC]

- It is sum total of I.C, FRC

- The values of these volumes & capacities are different in males & females.
- The average values of the various volumes & capacities are
  - T.V → 500 l
  - IRV → 3000 ml
  - ERV → 1100 ml
  - RV → 1200 ml
  - IC → 3500 ml
  - FRC → 2300 ml
  - VC → 4600 ml
  - TLC → 5800 ml [almost 6 liters]

Spirometry 00:12:18

- It is hand held device. It has a mouth piece which can be changed for each person to be used.
- The person is asked to forcefully expire into the spirometry after mouth piece maximal inspiration
- We get a volume – time plot after spirometry
- When μ forcefully expire 80-85% of expired air, will be happening in 1st second. This is called FEV_1
- FEV_1 >80% of V.C
- In pulmonology we can categories various disorders into obstructive, restrictive, pulmonary vascular disease by the help of volume time plot

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Obstructive	Restrictive
- COPD - Bronchial asthma - Predominant problem is expiratory air flow limitation.	- Interstitial lung disease - Predominantly characterized by inspiratory problem

Volume time plot

- Normal volume-time plot V_3 obstructive disease V-T plot
  - The shape of V.T plot in obstructive disease is a sloping one.
  - The FEV_1 is very less than normal plot.
  - FVC is slightly less than normal plot.
  - Most important parameter to look in a V-T plot is FEV_1/FVC ratio. It can differentiate obstructive & restrictive lung disease.
  - In obstructive lung disease both FEV_1 & FVC reduces. But more strikingly reduced is FEV_1, so FEV_1/FVC is decreased.
- Normal VT plot vs restrictive lung disease V-T plot
  - Here the total forced V.C is very less compared to the normal because lesser amount of air coming in & lesser amount of air going out
  - Here both FVC & FEV_1 are reduced.
  - The shape of restrictive lung disease V-T plot is like a miniature form of normal V-T plot
  - FEV_1/FVC value is normal (or) increased, because the more proportionate reduction will be in FVC
  - How much reduction in FEV_1/FVC in obstructive lung disease is

a. as per American thoracic x guidelines based on age & sex. Below the lower limit of normal is taken to be the criteria.
b. As per gold, the global initiative for obstructive lung disease the ratio is <0.7

- For restrictive lung disease the value is normal (or) increased

- When we do spirometry, the residual volume & capacity using it like FRC & TLC, they cannot be estimated by routine spirometry. For that we have to go for technique like nitrogen washout method, Body plethysmography.

DLCO 00:28:04

- Diffusion capacity for carbon monoxide.
- Diffusion capacity for C.O relies on 2 factors
  a. Integrity of alveolo capillary membrane
  b. Gas exchange surface area (at alveolar level)
- In this test we choose C.O, because it has high affinity for hemoglobin. So it is ideal to check diffusion across alveolo capillary membrane.
- In disorders like 1. ILD, the diffusion is affected & in 2. Anemia (Hb decreases) & In 3. Emphysema (surface area is affected) 4. Left sided heart disease & 5. Pulmonary vascular disease (P. HTN, P. Embolism)
  In the above cases there is decrease in diffusion [decreases DLCO]
- DLCO is increased in
  i. Polycythemia
  ii. Pulmonary hemorrhage.

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- Common causes of obstructive lung disease.
  - COPD
  - Asthma
  - Bronchiectasis
  - Cystic fibrosis
  - α_1 – Antitrypsin deficiency
  - Silicosis (early)
  - Bronchiolitis obliterans
- Common causes of restrictive lung disorder
  - Chest wall problem
  - Kyphosis
  - Ankylosing spondylitis
  - Morbid obesity
  - Myasthenia gravis
  - ILD
  - GBS
  - Sarcoidosis
  - Silicosis (late)
  - Hypersensitivity pneumonitis
- To differentiate obstructive & restrictive the most important parameter is FEV_1/FVC ratio.
  First check whether the ratio is above normal (or) below the lower limit.
  If ratio is higher, go for measurement of FVC Now the FVC > lower limit of normal (or) above the normal
  - If FEV_1/FVC is high & FVC is above lower limit of normal then we measure DLCO.
  - If DLCO is also normal the individual may be normal
  - If DLCO is abnormal the it is pulmonary vascular disorder

- If FEV_1/FVC ratio is higher FVC is low, than TLC is measured.
- The TLC in restrictive lung disease is smaller/lower.
- In restrictive lung disease to differentiate further
- We do DLOC, If DLCO is low → ILD, Pneumonitis
- DLOC is normal → chest wall & neuromuscular problems
- If TLC is normal (or) above lower limit of normal then there is possibility of early obstructive lung disease
- If FEV_1/FVC ratio is <0.7, we can consider obstructive lung disease.
- If PVC is above normal, TLC is reduced, there can be a scenario where we can get mixed defect. (restrictive & obstructive)

- In obstructive lung disease, to differentiate further go for DLCO
  - DLCO is low Emphysema
  - DLOC is normal, in asthma, chronic bronchitis

Flow – Volume Loops – 00:47:20

- Normal flow volume loop → on X-axis volume
  Y – axis volume
  The inspiration is represented in downward part
  Expiration is represented in upward part
- From TLC, the patient is expiring to R.V
- The peak is referred as peak expiratory flow rate
- The gap between TLC & RV is FVC

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Abnormalities of flow volume loop

- In obstructive lung disease predominantly expiration is affected, as it is expiratory air flow limitation.
- The descending limb of F-V loop almost has a concavity.
- In restrictive lung disease, the predominant is inspiratory problem, so inspiratory limb of loop is small, and as the amount of air taken in is less, so the amount of air going out will also be less.
  So, totally the loop is small
- In obstructive lung disease patient, in spirometry give bronchodilatory to the patient, because in case of bronchial asthma he may have B.D reversibility so after giving B.D, there may be an improvement in the pulmonary function tests.
- We can say there is B.D reversibility, If FEV_1 >12% (FEV_1 increases by 12%) (or) 200ml increases.
  And favours diagnosis of bronchial asthma.
- F-V loops in upper airway obstruction →
- Variable extra thoracic obstruction →
  Variable obstruct means it varies with phase of respiration & because here is outside the thorax
  E.g. – Vocal cord palsy
  - The prob in F-V loop is the inspiratory limb of the F-V loop, it is small, the expiratory limb appears normal
  - In variable in for thoracic obstruct, as in case of trachea malacia, it predominantly affects the expiratory limb.
  - In fixed airway obstruction. Example: Tracheal stenosis, here both expiratory & Inspiratory limb are small.

PULMONARY THROMBOEMBOLISM

Introduction 00:00:20

- Source of thrombus of thrombus is often a deep vein thrombosis.
- Veins involved
  - Soleal
  - Popliteal
  - Femoral
  - Iliac

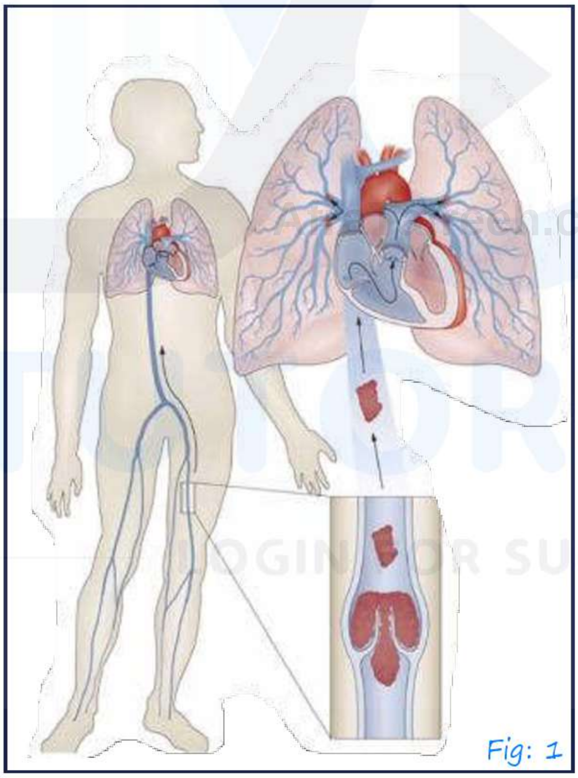

Fig: 1

- Thrombus formation at the site of venous valves because the normal streamline flow of blood interrupted.
- Often region of valves would serve as the NIDUS

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- Once thrombus formed it gets dislodged and travels via venous system through the IVC, enters (R) side of the heart and through pulmonary artery, enters the lungs
- For the formation of thrombus to happen - VIRCHOW'S TRIAD
  - Stasis Turbulence
  - Hypercoagulability
  - Endothelial injury

Virchow's triad: Clinical states predisposing to venous thrombosis

Stasis	- Immobility - Bed rest - Anaesthesia - Congestive heart failure/cor pulmonale - Prior venous thrombosis
Hypercoagulability	- Malignancy - Anticardiolipin antibody - Nephrotic syndrome - Essential thrombocytosis - Oestrogen therapy - Heparin-induced thrombocytopenia Inflammatory bowel disease

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	- Paroxysmal nocturnal haemoglobinuria - Disseminated intravascular coagulation - Protein C and S deficiencies - Antithrombin III deficiency
Vessel wall injury	- Trauma - Surgery

Pathophysiology 00:03:20

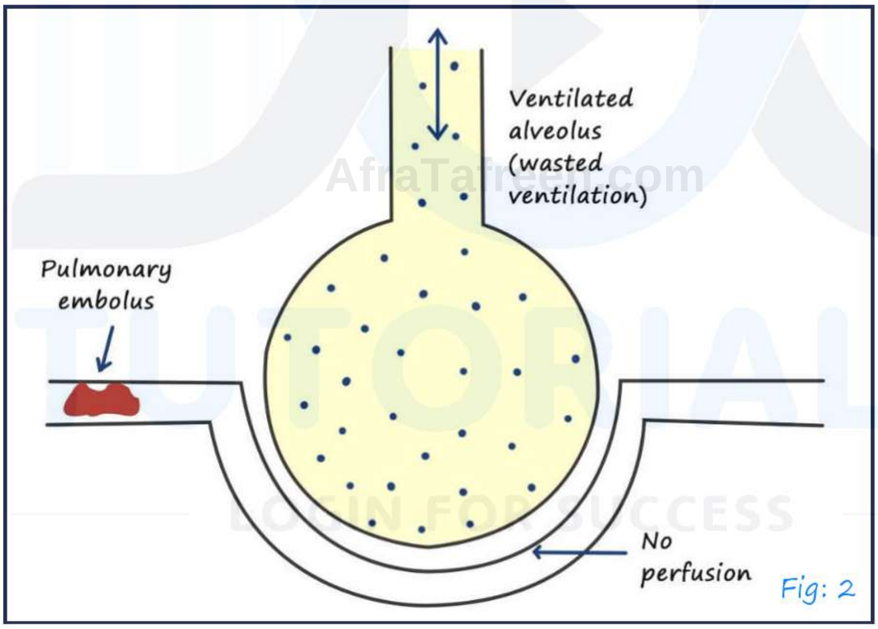

Fig: 2

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- No Perfusion
- ventilation perfusion mismatch Dead space ventilation
- Pulmonary hypoxemia
- Increased PAO_2- $PaO2$
- Pulmonary alveolar - arterial oxygen tension gradient
- Normal 5-15 mmHg

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- Increased pulmonary compliance Alveolar hyperventilation

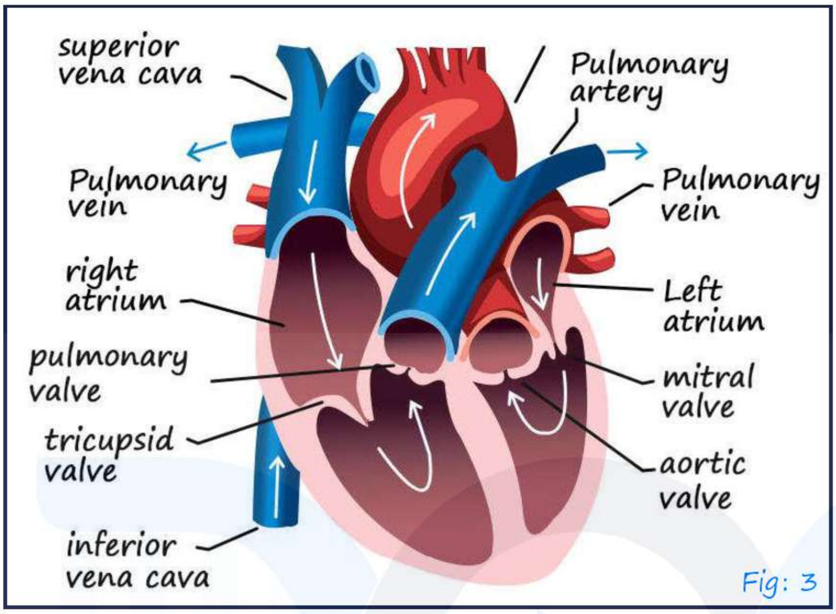

Fig: 3

- clot in pulmonary artery
- Obstruction of flow from ® ventricle through the pulmonary artery to the lungs
- Hypoxia
- Pulmonary vasoconstriction
- Pulmonary HTN
- (R) ventricular dilatation and dysfunction
- Acute cor pulmonale
- Elevated JVP (kussmaul's sign)
- LV end diastolic volume ↓
- ↓ co and systolic blood pressure

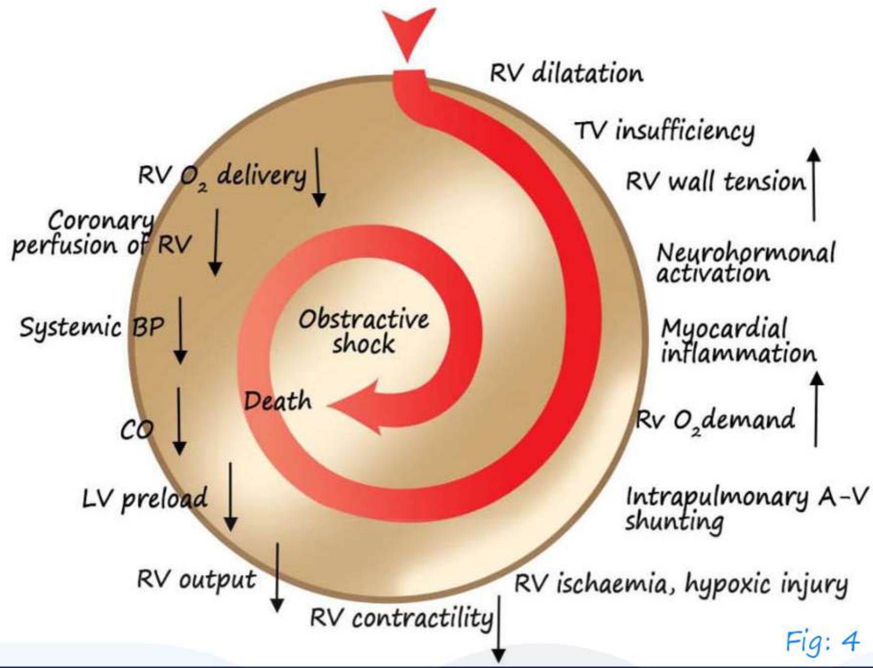

Fig: 4

Clinical features 00:21:46

- Low index pulmonary embolism
- Sub massive pulmonary embolism
- Massive pulmonary embolism
  - Decrease co and systolic blood pressure
  - Most common symptom – Dyspnea, Chest pain, haemoptysis
  - D/E –
  - Tachycardia
  - Hypotension
  - Tachypnea
  - increase JVP, pedal edema
  - Wide and fixed S2 split

Wells clinical prediction scoring

- Score ≥ 4 - high probability of pulmonary embolism

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Investigations and work up 00:31:16

1.D-dimer elevated (screening test)

- If D-dimer, less likely to be pulmonary thromboembolism

2.12 lead ECG → Sinus tachycardia S1, Q3 T3 pattern (specific pattern)

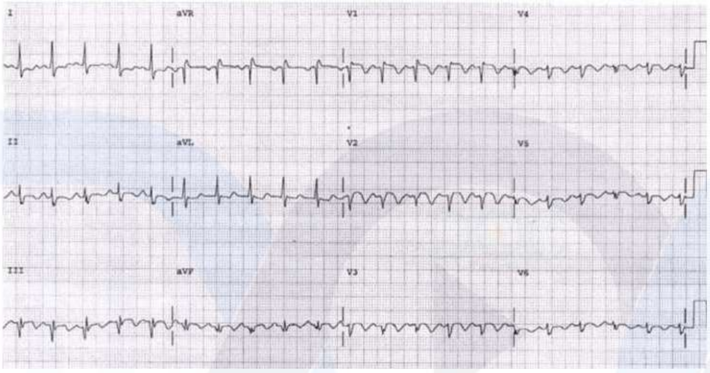

Fig: 5

- Prominent S wave in lead I
- Prominent Q wave in lead III
- T inversion in lead III

3.Toc: CTPA

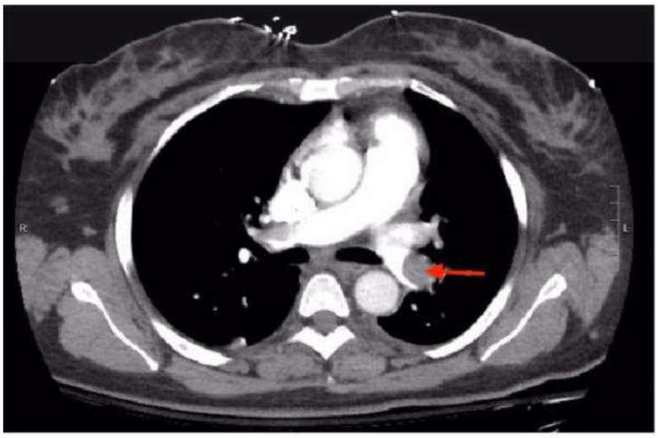

Fig: 6

- Filling defect

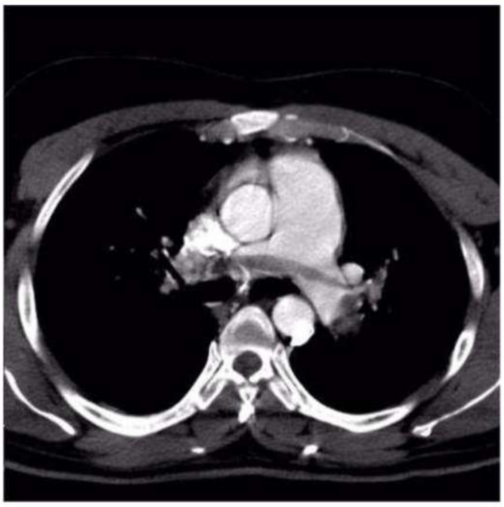

Fig: 7

- Saddle thrombus

4.V/Q scan: - using radio isotope

- Used where contrast is clinical infection

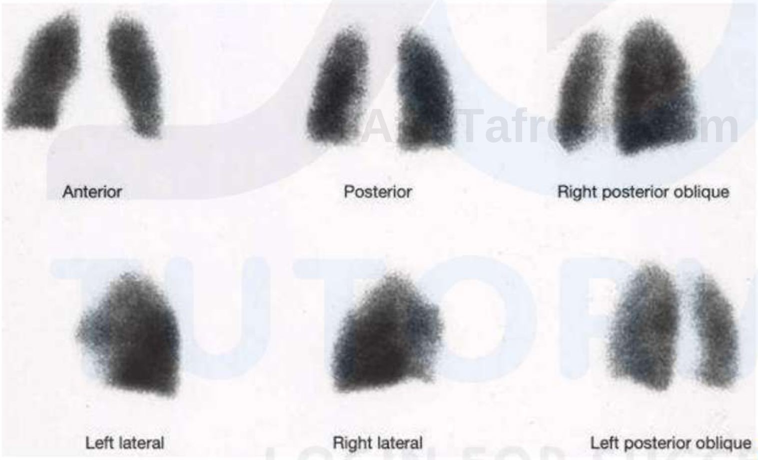

Fig: 8

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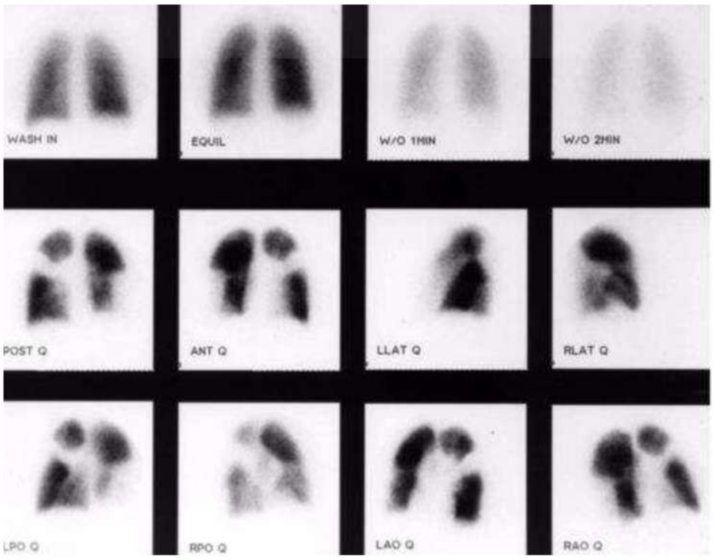

Fig: 9

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5.CXR -

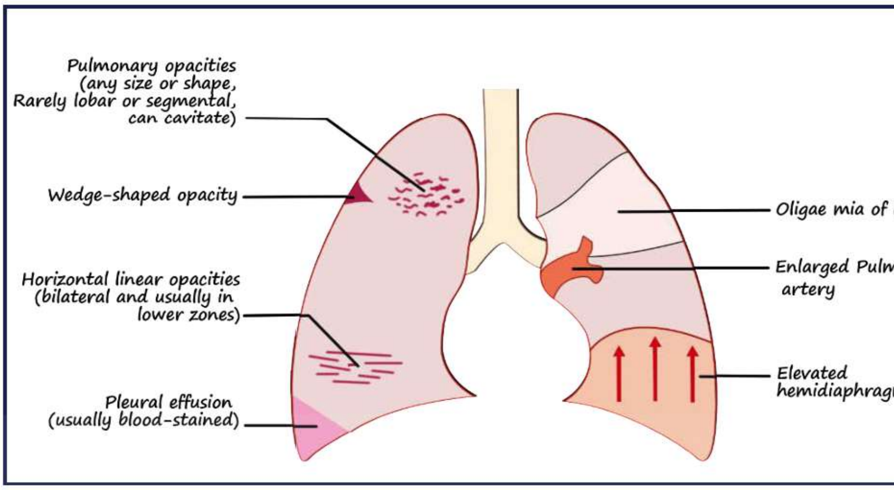

Fig: 10

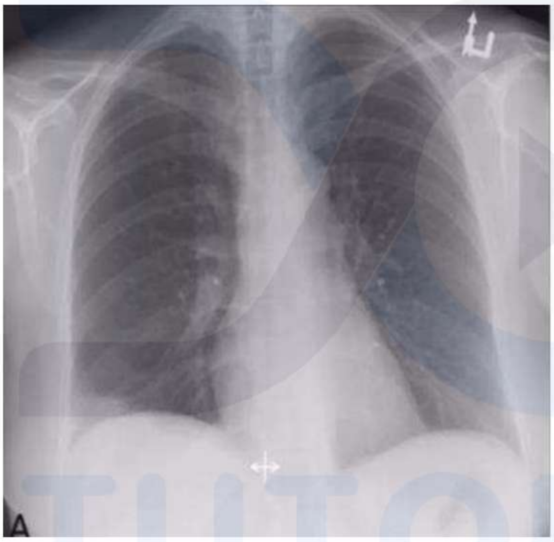

Fig: 11

- Peripheral wedge-shaped opacity

↓

HAMPTON'S HUMP

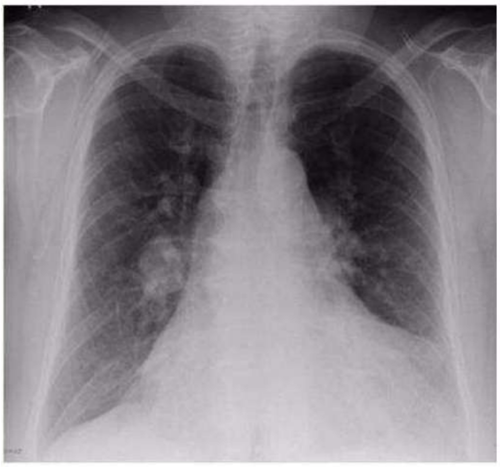

Fig: 12

- Dilated central pulmonary artery

↓

Fleischner's sign

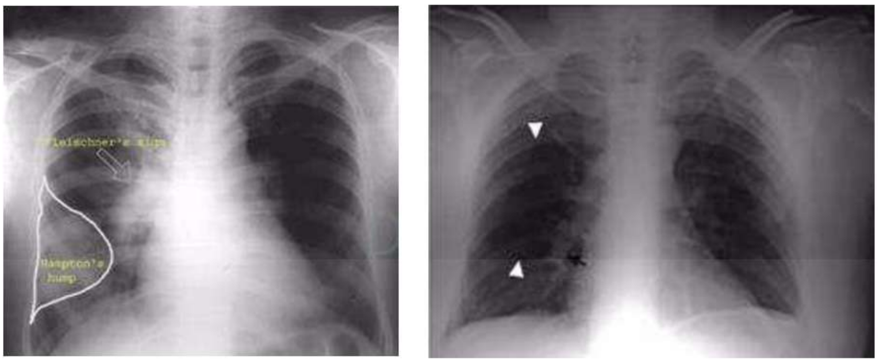

Fig: 13

Focal oligemia

↓

Westermark's sign

- Dilated descending pulmonary artery

↓

Palla's sign

6.Echo - RV hypokinesia - Mc Connell's

Treatment: 00:49:30

- 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European respiratory society (ERS)
  - The task forces the diagnosis and management of acute pulmonary embolism of the European society of cardiology (ESC)

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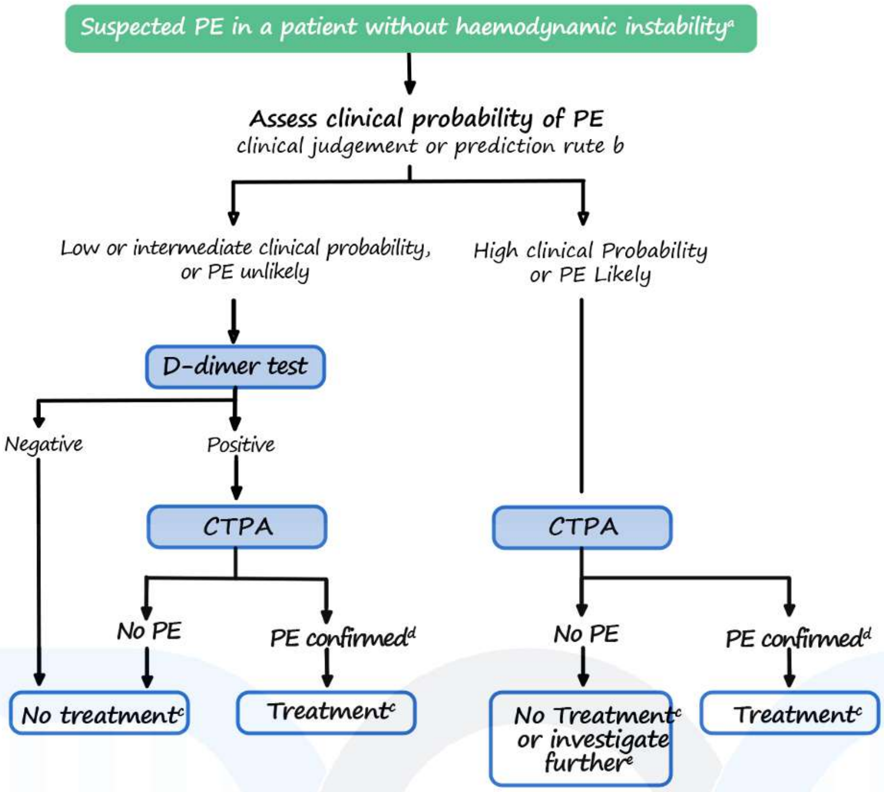

Definition of haemodynamic instability which delineates acute high-risk pulmonary embolism (One of the following clinical manifestations at presentation		
1.Cardiac arrest	2.Obstructive shock (68-70)	3.Persistent hypotension
Need for cardiopulmonary resuscitation	• Systolic BP <90mmHg or vasopressors required to achieve a BP ≥90mmHg despite adequate filling status • End organ hypoperfusion	• Systolic BP <90mmHg or systolic BP drop ≥40mmHg lasting longer than 15min and not caused by new onset

	(Altered mental status cold, clammy skin. oliguria/anuria; increased serum lactate)	arrhythmia, hypovolaemia or sepsis

Massive PE with hemodynamic instability

1.Thrombolysis

- Alteplase → 100mg over 2hrs
- Best result if thrombolysis within 48hours
- Can be done up to 14days

Thrombolytic regimes doses and contraindications

Molecular	Regimen	Contraindication to fibrinolysis
RTPA Streptokinase Urokinase	100 mg over 2h 0.6 mg/kg over 15 min (maximum dose 50 mg)" 250 000 IU as a loading dose over 30 min, followed by 100000 IU/h	**Absolute** History of haemorrhagic stroke or stroke of unknown origin Ischaemic stroke in previous 6 months Central nervous system neoplasm

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	over 12–24 h Accelerated regimen: 1.5 million IU over 2 h 4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg/h over 12–24 h Accelerated regimen: 3 million IU over 2 h	Major trauma, surgery, or head injury in previous 3 weeks Bleeding diathesis Active bleeding **Relative** Transient ischaemic attack in previous 6 months Oral anticoagulation Pregnancy or first post-partum week Non-compressible puncture sites Traumatic resuscitation Refractory hypertension (systolic BP >180 mmHg) Advanced liver disease Infective endocarditis Active peptic ulcer

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2.Anticoagulation

- LMWH
- Fondaparinux
- UPH

↓

Antidote- protamine sulfate

- Warfarin
- NOAC → Preferred
- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban

Target INR - 2-3

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Clinical infection: Anticoagulation/Recurrent episodes

↓

IVF (Inferior vena caval filter)

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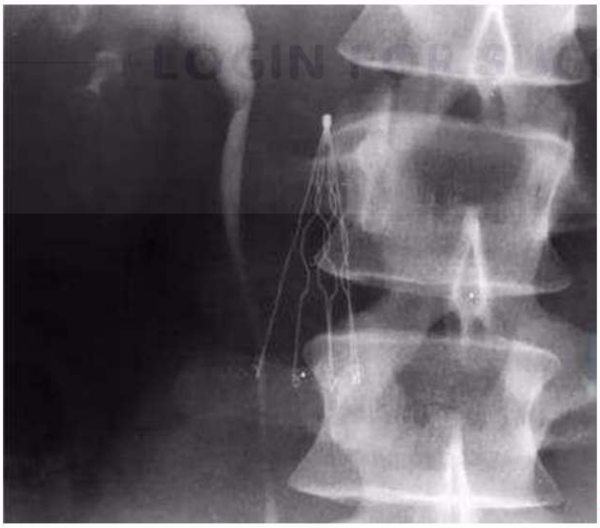

Fig: 15

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PNEUMONIA

- Infection of lung parenchyma – may involve Alveoli
  Interstitial
- Can be because of – Bacteria
  Virus
  Fungus
  Protozoa

Classification of pneumonia 00:02:30

i. Community acquired pneumonia
ii. Hospital acquired pneumonia
iii. Ventilator associated pneumonia
iv. Health care associated pneumonia
↓
Removed as per IDSA- ATS guideline in 2019

Community Acquired Pneumonia (CAP) 00:04:42

Microbial cause of community – Acquired pneumonia, by site of care		
	Hospitalized patients	
Outpatients	Non – ICU	ICU
Streptococcus	S. Pneumoniae	S. Pneumoniae
Pneumoniae	M. Pneumoniae	Staphylococcus aureus

Mycoplasma pneumoniae	Chlamydia pneumoniae	Legionella spp.
Haemophilus influenzae	H. influenzae	Gram negative bacilli
C. pneumoniae	Legionella spp.	H. influenzae
Respiratory viruses	Respiratory viruses	Respiratory viruses
Influenza A and B viruses, human metapneumovirus, adenovirus, respiratory syncytial viruses, parainfluenza viruses.		

CAP

Typical ↓

- Strep pneumonia
- H. influenza
- Staphureus
- Klebsiella
- Pseudomonas

Atypical ↓

- Mycoplasma
- Chalmydia pneumonia
- Legionella
- Adenovirus
- RSV
- Covid – 19
- Influenza

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- Cavitations] Common with staphaureus
  Pneumatoceles Klebsiella

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Risk factors for pathogens resistant to usual therapy for community acquired pneumonia		
Multidrug – resistant Gram – negative bacteria and MRSA	**Nosocomial MRSA**	**Community – Acquired MRSA**
Hospitialization ≥ 2 days in previous 90 days	Hospitialization ≥ 2 days in previous 90 days	Cavitary infiltrate or necrosis
Use of antibiotics in previous 90 days	Use of antibiotics in previous 90 days	Gross hemoptysis
Immunosuppression	Chronic hemodialysis in previous 30 days	Neutropenia
Nonambulatory status	Documented prior MRSA	Erythematous rash
Tube feedings	Colonization	Concurrent influenza
Gastric acid suppression	Congestive heart failure	Young, previously healthy status
Sever COPD or bronchiectasis	Gastric acid suppression	Summer-month onset

Anaerobes causing pneumonia

- In normal scenario, though you have anaerobe colonization, the host defenses, the branched tracheobronchial tree & the macrophages in the alveoli will protect against infection.
- Suppose, you have altered sensorium, Gag reflex, cough reflex are compromised → free passage of organisms to alveoli.
- Chance of anaerobic infection is high in immunosuppression

Epidemiologic factors suggesting possible causes of community acquired pneumonia	
Factor	**Possible pathogen(s)**
Alcoholism	Streptococcus pneumoniae, Oral anaerobes, Klebsiella pneumoniae, Acinetobacter spp., Mycobacterium tuberculosis
COPD and/or smoking	Haemophilus influenzae, Pseudomonas aeruginosa, Legionella spp., S. pneumoniae, Moraxella catarrhalis, Chlamydia pneumoniae

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Structural lung disease (e.g., bronchiectasis)	P. aeruginoasa, Burkholderia cepacian, Staphylococcus aureus
Dementia, stroke, decreased level of consciousness	Oral anaerobes, gram-negative enteric bacteria
Lung abscess	CA-MRSA, oral anaerobes, endemic fungi, M. tuberculosis, atypical mycobacteria
Travel to Ohio or St. Lawrence River valley	Histoplasma capsulatum
Travel to southwestern United states	Hantavirus, Coccidioides spp.
Travel to Southeast Asia	Burkolderia pseudomallei, avian influenza virus
Stay in hotel or on cruise	Legionella spp.

- Pneumonia that presents with hyponatremia → Legionella

Pathology

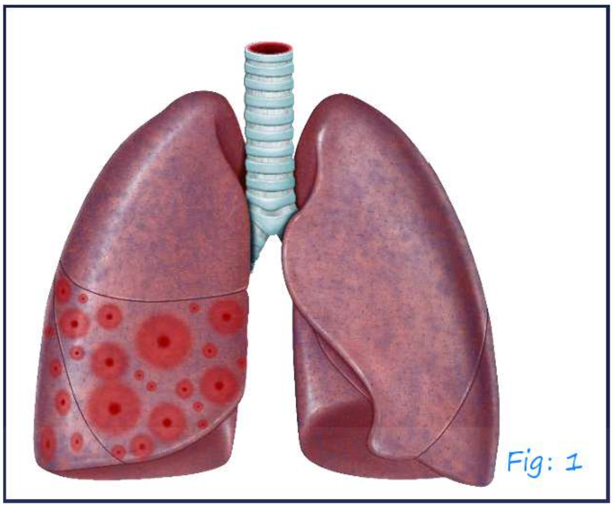

Fig: 1

- Infection of lung parenchyma produce exudation & alveoli will be filled with exudates
- 2 types → Bronchopneumonia → patchy patchy areas of consolidation

  Lobar pneumonia → Uniform consolidation

Fig: 2

- Disease is primarily at alveolar level

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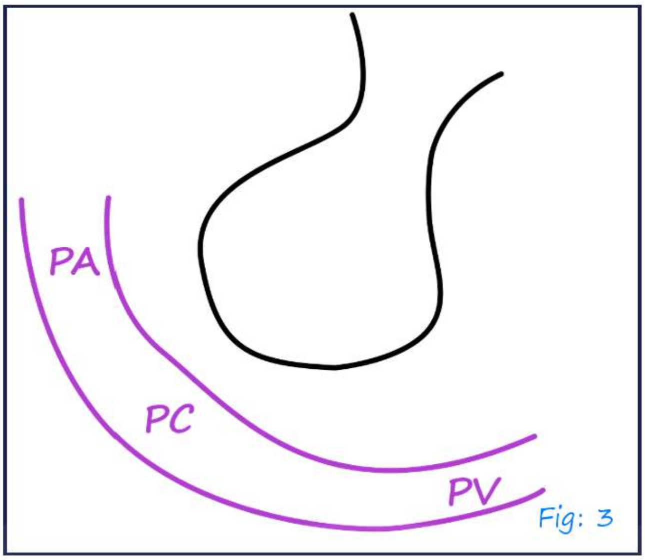

Fig: 3

Stages in pathogenesis of lobar pneumonia

00:35:40

- Stage 1 – Stage of congestion
- Stage 2 – Stage of red hepatization
- Stage 3 – Stage of grey hepatization
- Stage 4 – Stage of resolution
- Stage of congestion – leaky alveolocapillary membrane proteinaceous fluid reached alveoli Alveolar flooding
- Stage of red hepatization – RBC's + poly morphoneutrophilis gain access to alveoli solidification of lung parenchyma
- Stage of grey hepatization – Breakdown products or RBC + PMN
- Main line of defense in alveoli – pulmonary macrophage

Complications

- Necrosis
- Cavitation
- Pneumatoceles
- Emphysema
- Abscess

Clinical features

- Fever → pyrogenic cytokines like IL-1, TNF α involved
- Cough – dry cough with rusty sputum

  ↓

  Purulent sputum
- Breathlessness because of alveolar flooding

  ↓

  PaO_2 decreases
- Type I respiratory failure
- Normally/Decreased $PaCO_2$

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Atypical features

- Chest pain
- Abdominal pain
- Mycoplasma pneumonia often referred to as walking pneumonia.
- Hemolytic anemia
- SJS

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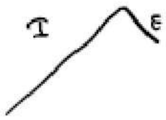
- O/E – Febrile

  Tachypnea

  Tachycardia

  Increases vocal fremitus & resonance

  Bronchial breathing



Vesicular breathing

Bronchial breathing

  Crepitations

  Bronchophony

  Egophony

  Whispering pectoriloquy

- Pneumonia may be associated with parapneumonic effusion

Confusion

Urea > 7 mmol/L

Respiratory rate ≥ 30/min

Blood pressure (SBP < 90mmHg or DBP ≤ 60 mmHg)

Age ≥ 65 years

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Score 1 point for each features present

CURB – 65 score	0 or 1	2	3 or more
	↓	↓	↓
	Likely suitable for home treatment	Consider hospital supervised treatment	Manage in hospital as severe pneumonia Assess for ICU admission especially if CURB-65 score = 4 or 5

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CURB - 65

- Confusion 1
- BUN > 20mg % - 1
- Respiratory rate > 30-1
- BP – systolic < 90 (or) -1
  Diastolic < 60
- Age >65

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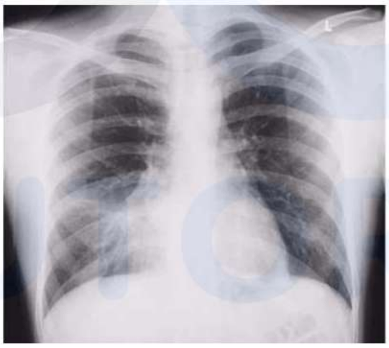
Investigations

- CBC – leukocytosis
- ESR increases
- CRP increases
- RFT
- LFT
- Sputum analysis → Gram stain
  Culture
  RT-PCR
- Blood culture
- CXR
- CT thorax – complicated/Non resolving pneumonia



Right middle lobe consolidation

silhouette's sign Fig: 4

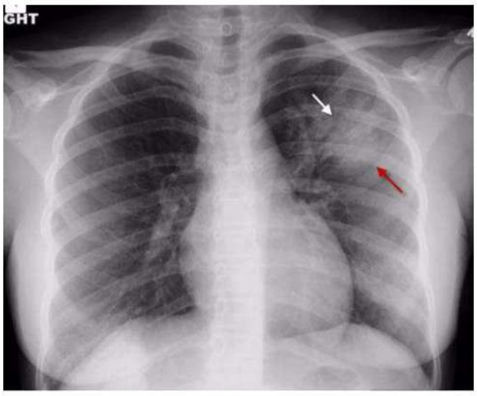
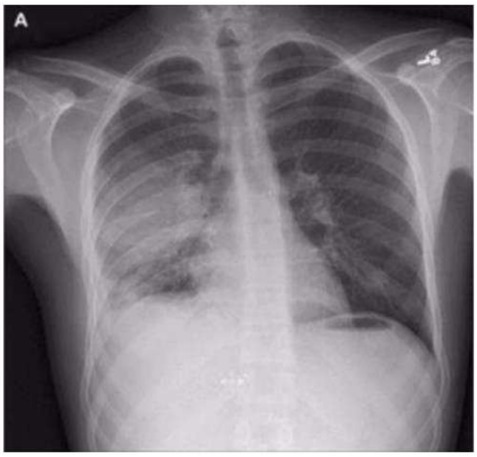


Fig: 5

Air bronchogram – lobar consolidation



Pneumonia with parapneumonic effusion

↓

Story dullness present

Fig: 6

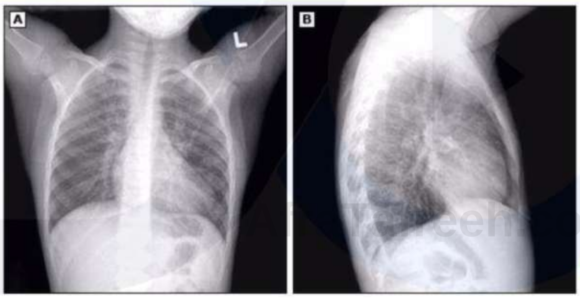


Fig: 7

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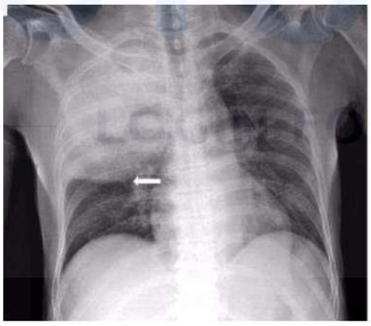

Fig: 8

Bulging fissure sign → commonly attributed to Klebsiella

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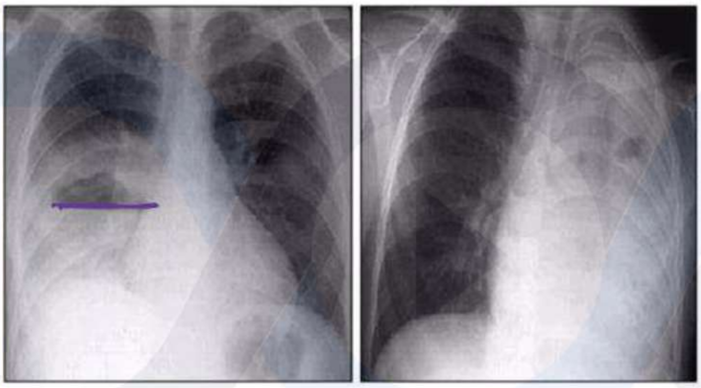
Fig: 9

Red currant jelly sputum – Klebsiella



Abscess, Necrotising pneumonia Fig: 10

Fig: 11

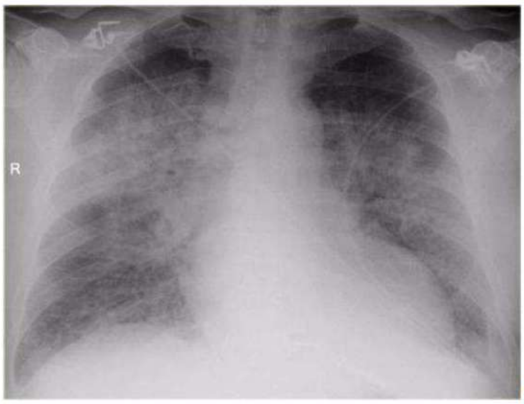


Fig: 12

- In early cases, X-ray might be normal
- Urinary antigen testing for – Legionella

  – Pneumococcus

Treatment of CAP

American Thoracic Societ Documents

- Diagnosis and Treatment of Adults with Community-acquired Pneumonia
- An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America
- a Joshua P. Metlay", Grant W. Waterer". Ann C. Long, Antonio Anzueto, Jan Brozek, Kristina Crothers, Laura A. Cooley. Nathan C. Dean, Michael J. Fine, Scott A. Flanders, Marie R. Griffin, Mark L. Metersky, Daniel M. Musher, Marcos L. Restrepo, and Cynthia G. Whitney: on behalf of the American Thoracic Society and Infectious Diseases Society of America
- The official clinical practice guideline was approved by the American thoracic society may 2019 and the infectious disease s society of America august 2019

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Outpatients

1. Previously healthy and no antibiotics in past 3 months
   - A macrolide [clarithromycin (500 mg PO bid) or azithromycin (500 mg PO once, then 250 mg qd)] or
   - Doxycycline (100 mg PO bid)

2. Comorbidities or antibiotics in past 3 months: select an alternative from a different class
   - A respiratory fluoroquinolone [moxifloxacin (400 mg PO qd), gemifloxacin (320 mg PO qd), levofloxacin (750 mg PO qd)] or
   - A β-lactam [preferred: high-dose amoxicillin (1 g tid) or amoxicillin/ clavulanate (2 g bid); alternatives: ceftriaxone (1-2 g IV qd), cefpodoxime (200 mg PO bid), or cefuroxime (500 mg PO bid)] plus a macrolide

CAP (Empirical)

- OP based
- IP based Non-ICU
- IP based ICU

• Patients, Non-ICU

- A respiratory fluoroquinolone [e.g., moxifloxacin (400 mg PO or IV qd) or levofloxacin (750 mg PO or IV qd)]
- A B-lactam [e.g., ceftriaxone (1-2 g IV qd), ampicillin (1-2 g IV q4-6h), cefotaxime (1-2 g IV q8h), ertapenem (1 g IV qd)] plus a macrolide [e.g., oral clarithromycin or azithromycin as listed above or IV azithromycin (1 g once, then 500 mg qd)]

• Inpatients, ICU
  - A β-lactam [e.g., ceftriaxone (2 g IV qd), ampicillin-sulbactam (2 g IV q8h), or cefotaxime (1-2 g IV q8h)] plus either azithromycin or a fluoroquinolone (as listed above for inpatients, non-ICU)

Recommendation	2007 ATS / IDSA Guideline	2019 ATS / IDSA Guideline
Sputum culture	Primarily recommended in patients with severe disease	Now recommended in patients with severe disease as well as in all inpatients empirically treated for MRSA or Pseudomonas aeruginosa
Blood culture	Primarily recommended in patients	Now recommended in patients with severe disease as well

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	with severe disease	as in all inpatients empirically treated for MRSA or P. aeruginosa
Macrolide monotherapy	Strong recommendation for outpatients	Conditional recommendation for outpatients based on resistance levels
Use of procalcitonin	Not covered	Not recommended to determine need for initial antibacterial therapy
Use of corticosteroids	Not covered	Recommended not to use. May be considered in patients with refractory septic shock
Use of healthcare-associated pneumonia category	Accepted as introduced in the 2005 ATS/IDSA hospital-acquired and ventilator-associated pneumonia guidelines	Recommend abandoning this categorization. Emphasis on local epidemiology and validated risk factors to determine need for MRSA or P. aeruginosa coverage. Increased emphasis on de-escalation of treatment if cultures are negative

Standard empiric therapy for severe CAP	B-Lactam/macrolide and B-lactam/fluoroquinolone combinations given equal weighting	Both accepted but stronger evidence in favor of B-lactam/macrolide combination
Routine use of follow-up chest imaging	Not addressed	Recommended not to obtain. Patients may be eligible for lung cancer screening, which should be performed as clinically indicated

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- If organism is pseudomonas → Meropenem
  Piperacillin – Tozabactam
- MRSA → Vancomycin
  Linezolid

Treatment of ventilator associated pneumonia/ HAP 01:12:48

- Organisms – Pseudomonas
  Acinetobacter
  MRSA

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Empirical Antibiotic Treatment of Hospital – Acquired and Ventilator – Associated Pneumonia		
No risk factors for resistant gram negative protein	Risk factors resistant Gram – negative Pathogen (Choose one from each column)	
- Piperacillin-tazobactam (4.5 g IV q6h) - Cefepime (2 g IV q8h) - Levofloxacin (750 mg IV q24h)	- Piperacillin-tazobactam (4.5 g IV q6h') - Cefepime (2 g IV q8h) - Ceftazidime (2 g IV q8h) - Imipenem (500 mg IV q6hb) - Meropenem (1 g IV q8h)	- Amikacin (15-20 mg/kg IV q24h) - Gentamicin (5-7 mg/kg IV q24h) - Tobramycin (5-7 mg/kg IV q24h) - Ciprofloxacin (400 mg IV q8h) - Levofloxacin (750 mg IV q24h) - Colistin (loading dose of 5 mg/kg IV followed by maintenance doses of 2.5 mg x [1.5 x CrCl + 30] IV q12h) - Polymyxin B (2.5 - 3.0 mg/kg per day IV in 2 divided doses)

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BRONCHIAL ASTHMA

Introduction 00:00:10

- Obstructive lung disease characterized by reversible airway hyper responsiveness (AHR)

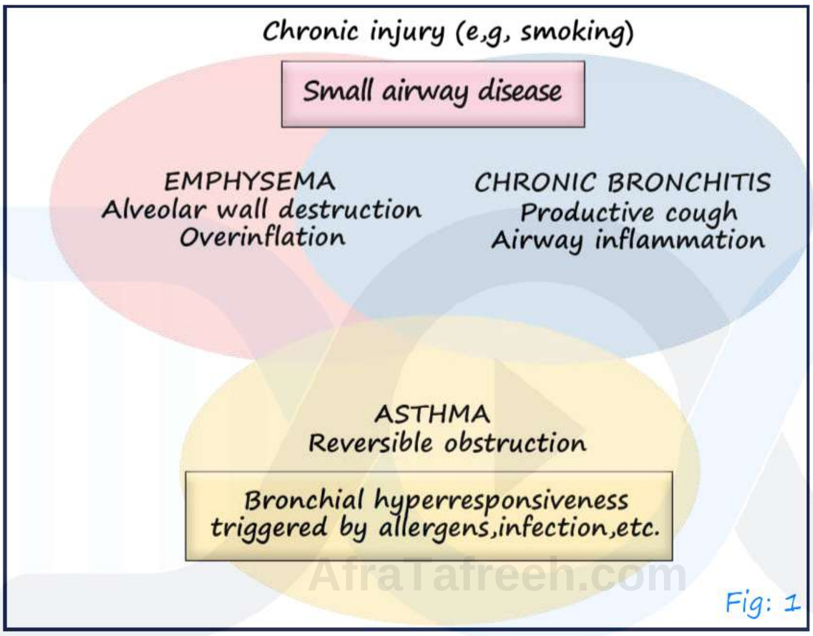

Fig: 1

Risk Factors and Triggers Involved in Asthma	
ENDOGENOUS FACTORS	ENVIRONMENTAL FACTORS
Genetic predisposition	Indoor allerg
Atopy	Outdoor allergens
Airway hyperresponsiveness	Occupational sensitizers
Gender	Passive smoking
Ethnicity	Respiratory infections

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Obesity	Air pollution (diesel particulates, nitrogen oxides)
Early viral infections	Diet
TRIGGERS	
Allergens	
Upper respiratory tract viral infections	
Exercise and hyperventilation	
Cold air	
Sulfur dioxide and irritant gases	
Drugs (β-blockers, aspirin)	
Stress	
Irritants (household sprays, paint fumes)	

- Exercise induced asthma
  - Thermal theory
  - Osmotic theory

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Etiopathogenesis 00:03:00

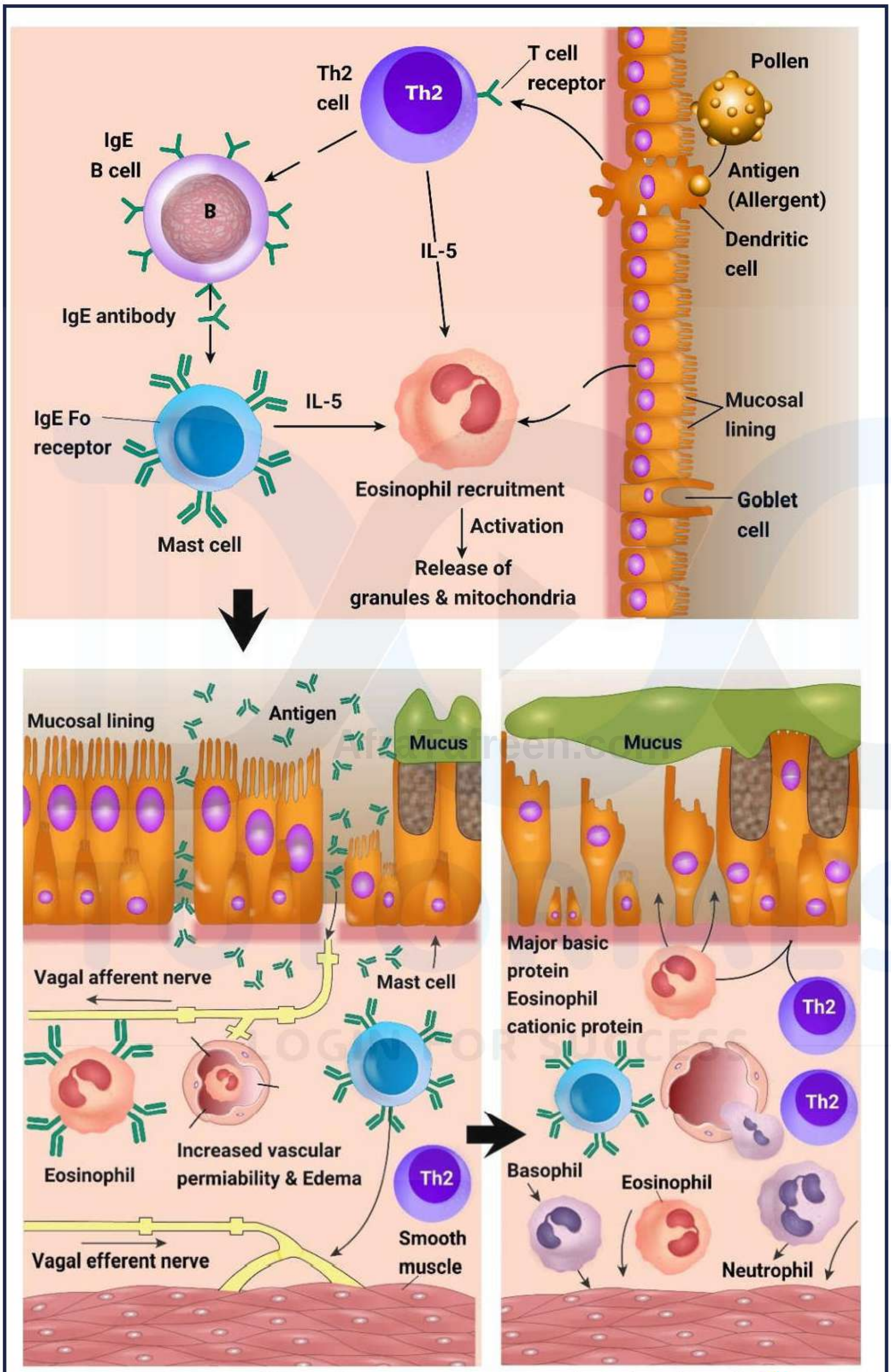

Fig: 2

- IL – 5 eosinophil activating cytokine

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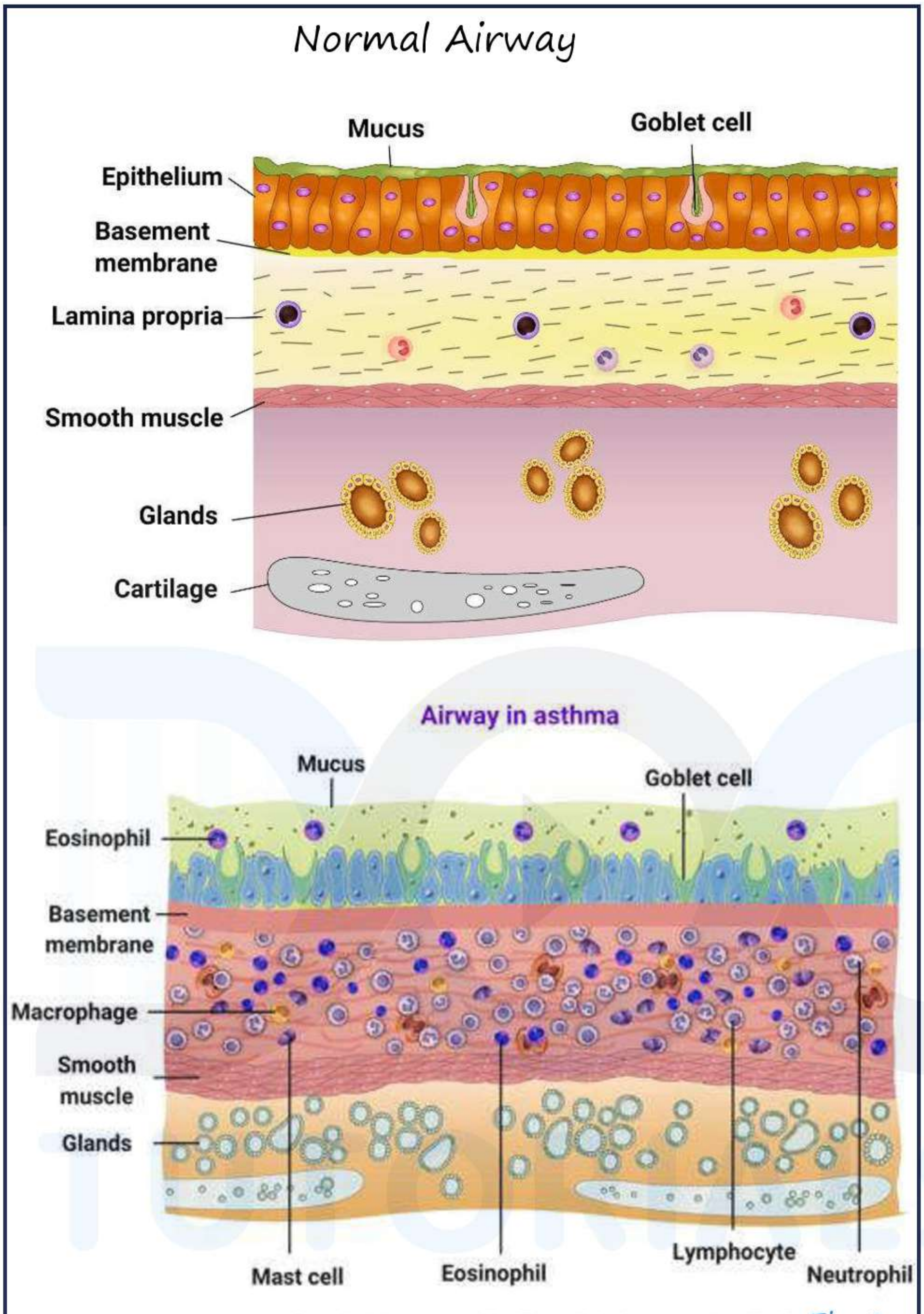

Fig: 3

- Cursctiman spirals → basophilic muscous plugs

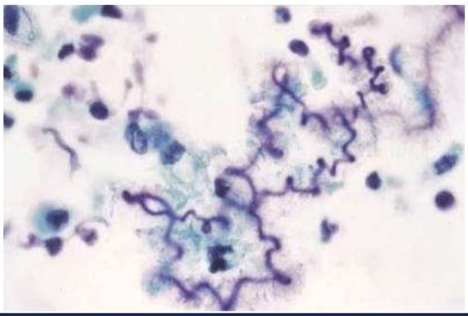

Fig: 4

- Charcot leyden crystals → degradation product of eosinophils

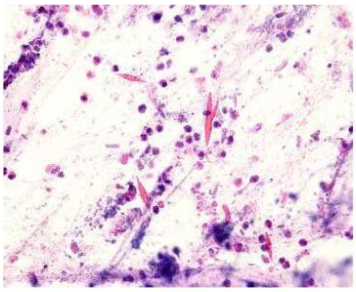

Fig: 5

Inflammatory cells

Mast cells

Eosinophils

TH2 cells

Basophils

Neutrophils

Platelets

Structural cells

Epithelial cells

Smooth muscle cells

Edothelial cells →

Fibroblasts

Nerves

Mediators

Histamine

Leukotrienes

Prostanoids

PAF

Kinins

Adenosine

Endothelins

Nitric oxide

Cytokine →

Chemokines

Growth factors

Effects

Bronchospasm

Plasma exudation

Mucus secretion AHR

Structural changes

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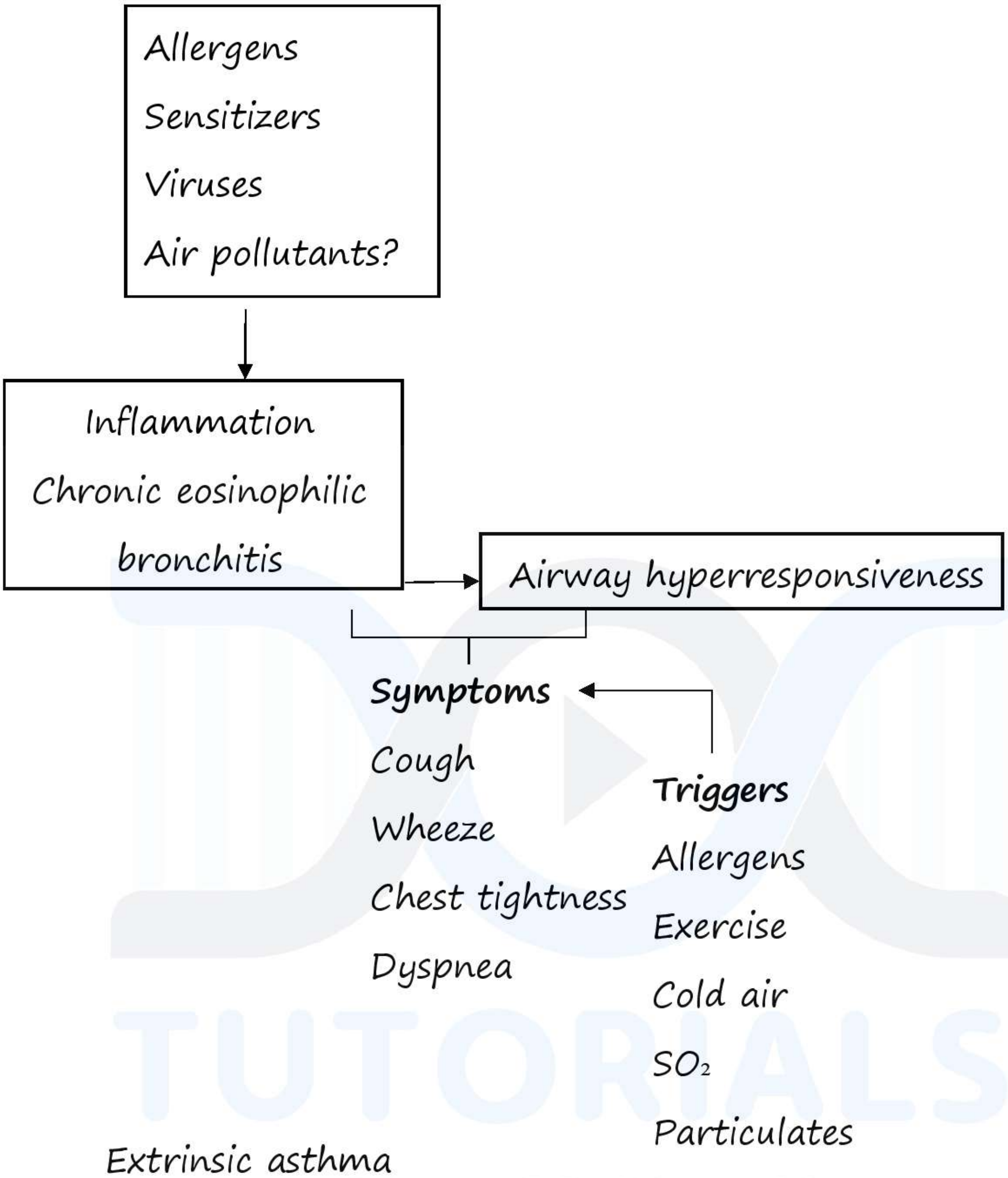

Extrinsic asthma

- Immunologically mediated

Points	Extrinsic	Intrinsic
1. Age	Early or childhood	Middle age or late onset
2. History of allergy	Usually present	Absent
3. Precipitating allergen	Present	Absent

4. Atopy	Atopic individual	Non atopic
5. Family history of asthma, rhinitis, eczema, etc.	Usually present	Usually absent
6. Skin prick test	Usually positive	Usually negative
7. Serum IgE	High	Normal

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- Aspinin – trigger for intrinsic asthma

  Samter's triad

  - Aspirin intolerance
  - Asthma
  - Nasak polyps

- 2019 – GINA guidelines (Global initiative for asthma)

Fig: 6

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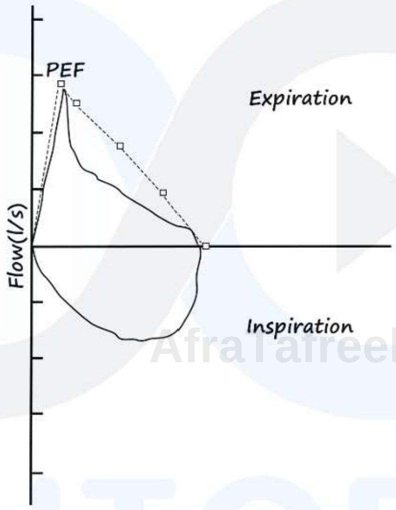
Diagnosis: 00:25:30

CRITERIA FOR MAKING THE DIAGNOSIS OF ASTHMA
Features used in making the diagnosis of asthma
1. A history of variable respiratory symptoms
Typical symptoms are wheeze, shortness of breath, chest tightness, cough: People with asthma generally have more than one of these symptoms,
• The symptoms occur variably over time and vary in intensity,
• The symptoms often occur or are worse at night or on waking,
• Symptoms are often triggered by exercise, laughter, allergens or cold air,
Symptoms often occur with or worsen with viral infections.
2. Evidence of variable expiratory airflow limitation
• At least once during the diagnostic process (example: when FEV_1 is low), document that the FEV/FVC ratio is below the lower limit of normality.
Document that variation in lung function is greater than in healthy people. For example, excess variability is recorded if:
o FEV_1 increases by >200 mL and >12% of the baseline value (or in children, increases from baseline by 12% of the predicted value) after

inhaling a bronchodilator. This is called significant bronchodilator responsiveness or reversibility.
o Average daily dismal PEF variability is >10% (in children, >13%)
o FEV, increases by more than 12% and 200 mL from baseline (in children, by >12% of the predicted value) after 4 weeks of anti-inflammatory treatment (outside respiratory infections).



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Treatment: 00:35:00

Goals of asthma treatment	
Few asthma symptoms	Symptom control
No sleep disturbance	
No exercise limitation	
Maintain normal lung function	Risk reduction
Prevent flare-ups (exacerbations)	
Prevent asthma deaths	
Avoid medication side-effects	

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Level of asthma symptom control				
In the past 4 weeks, has the patient had	Well controlled		Partly controlled	Un controlled
Daytime symptoms more than twice/week?	Yes/No	None of these	1-2 of these	3-4 of these
Reliever needed more than twice/week?	Yes/No			
Any night waking due to asthma?	Yes/No			
Any activity limitation due to asthma?	Yes/No			

Asthma
Controller medication
Add-on controller medication
Reliever medication

Controller medication
Inhaled corticosteroids (ICS)
OCS and long-acting beta 2 agonist (LABA) Bronchodilator combinations (ICS – LABA)
Leukotriene modifiers
Chromones

Low, Medium and High dose of ICS			
Inhaled corticosteroid	Adult and Adolescent		
	Low(mcg)	Medium (mcg)	High (mcg)
Beclomethasone dipropionate	100-200	>200-400	>400
Budesonide (DPI	200-400	>400-800	>800
Fluticasone propionate (DPI)	100-250	>250-500	>500
Fluticasone propionate (HFA)	100-250	>250-500	>500
Triamcinolone acetonide	400-1000	>1000-2000	>2000

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Controller Medication
➤ICS and long-acting beta2 agonist
bronchodilator combinations (ICS-LABA)
➤Beclomethasone-formoterol
Budesonide-formoterol
Fluticasone propionate-formoterol
➤Fluticasone propionate-salmeterol
Fluticasone furoate-vilanterol

- Maximum evidence for positive benefit is with budesonide – formoterol

Controller Medication
Leukotriene modifiers
Montelukast
Pranlukast
Zafirlukast
Zileuton
Chromones
Sodium cromoglycate
Nedocromil sodium

- 2020 → FDA black box warning for Montelukast

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Add – on controller medication
Long-acting anticholinergic
Anti-IgE
Anti-IL5
Anti-IL5R
Anti-IL4R
Systemic corticosteroids

Add – on controller medication
• long-acting anticholinergic (At Step 4 or 5 with a history of exacerbations despite ICS ± LABA)
Tiotropium
• Anti-IgE (with severe allergic asthma uncontrolled on high dose ICS-LABA)
Omalizumab

Add – on controller medication
• Anti-IL5 & Anti-ILSR (Severe eosinophilic asthma uncontrolled on high dose ICS-LABA)
- Mepolizumab & Reslizumab
- Benralizumab
• Anti-IL4R (Severe eosinophilic asthma uncontrolled on high dose ICS LABA, or requiring
- Dupilumab

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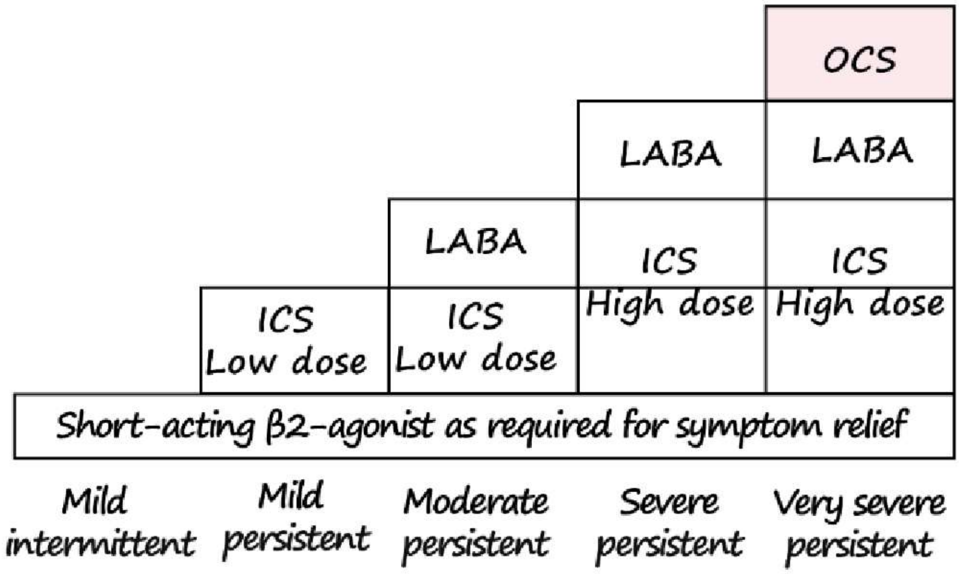
Add-on Controller Medication
systemic corticosteroids
prednisolone
hydrocortisone
Methylprednisolone

Reliever medication
Short-acting inhaled beta2-agoint
Low-dose ICS-formoterol
Short-acting anticholinergics

Stepwise therapy:

- For patients with mild, intermittent asthma, a SABA is all that is required. However, use of a reliever medication more than twice a week indicates the need for regular controller therapy. The treatment of choice for all patients is an ICS given twice daily. It is usual to start with an intermediate dose (example: 200 bid of [beclomethasone dipropionate] BDP) or equivalent and to decrease the dose if symptoms are controlled after three months. If symptoms are not controlled, a LABA should be added, which is most conveniently given by switching to a combination inhaler.



GIN 19-landmark changes in asthma management
For safety, GINA no longer recommends SABA-maltreatment for Step 1
• This decision was based on evidence that SABA-only treatment increases the risk of severe exacerbations, and that adding any ICS significantly reduces the risk
GINA now recommends that all adults and adolescents with asthma should receive ICS-containing controller treatment, to reduce the risk of serious exacerbations
• The ICS can be delivered by regular daily treatment or, in mild asthma, by as-needed low dose ICS-formoterol
This is a population-level risk reduction strategy
• Other examples: statins, anti-hypertensives
• Individual patients may not necessarily experience (or be aware of) short-term clinical benefit
• The aim is to reduce the probability of serious adverse outcomes at a population level

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Background to changes in 2019-the risks of SABA-only treatment
Regular or frequent use of SABA is associated with adverse effects
•B-receptor downregulation, decreased broncho protection, rebound hyperresponsiveness, decreased bronchodilator response (Hancox, Respir Med 2000)
•Increased allergic response, and increased eosinophilic airway inflammation (Aldridge, AJRCCM 2000)
Higher use of SABA is associated with adverse clinical outcomes
•Dispensing of 23 canisters per year (average 1.7 puffs/day) is associated with higher risk of emergency department presentations (Stanford, AAAI 2012)
•Dispensing of 212 canisters per year is associated with higher risk of death (Suisse, AJRCCM 1994

Box3-5A

Adults & adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response

Symptoms
Exacerbations
Side effects
Lung function
Patient satisfaction

Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors including lung function)
Comorbidities
inhaler technique & adherence
Patient preferences and goals

Treatment of modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medicanons (adjust down or up)
Education skills training

Asthma medication options:
Adjust treatment up and down for Individual patient needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	As-needed low dose ICS-formoteral*	Daily low dose inhaled corticosteroid (ICS) or as-needed low dose ICS-formateral*	low dose ICS-LABA	Medium dose ICS-LABA	High dose ICS-LABA refer for phenotypic assessment +add on therapy, e.g tiotropium anti IgE, anti IL5/5R anti IL-4R
Other controlar options	Low dose ICS taken whenever SABA is taken	Daily leukotriene receptor antagonist(LTRA)or low dose ICS taken whenever SABA taken †	Medium dose ICS,or low dose ICS+LTRA#	High dose ICS, ad on tiotropium or add on LTRA#	Add Low-dose OGS but consider side-effects
PREFERRED RELIEVER	As-needed low dose ICS-formoterol *		As-needed low dose ICS-formoterol for patients prescribed maintenance and relever therapy ‡		
Other redever option	As-needed short-acting β_2-agoniat (SABA)				

* data only with budesonide-formoterol (bad-form)
† separate or combination ICS and SABA inhalers
‡ Low-dose ICS form is the reliever for patients prescribed bud-form or BDP-form maintenance and relever therapy
\# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV >70 % predicted

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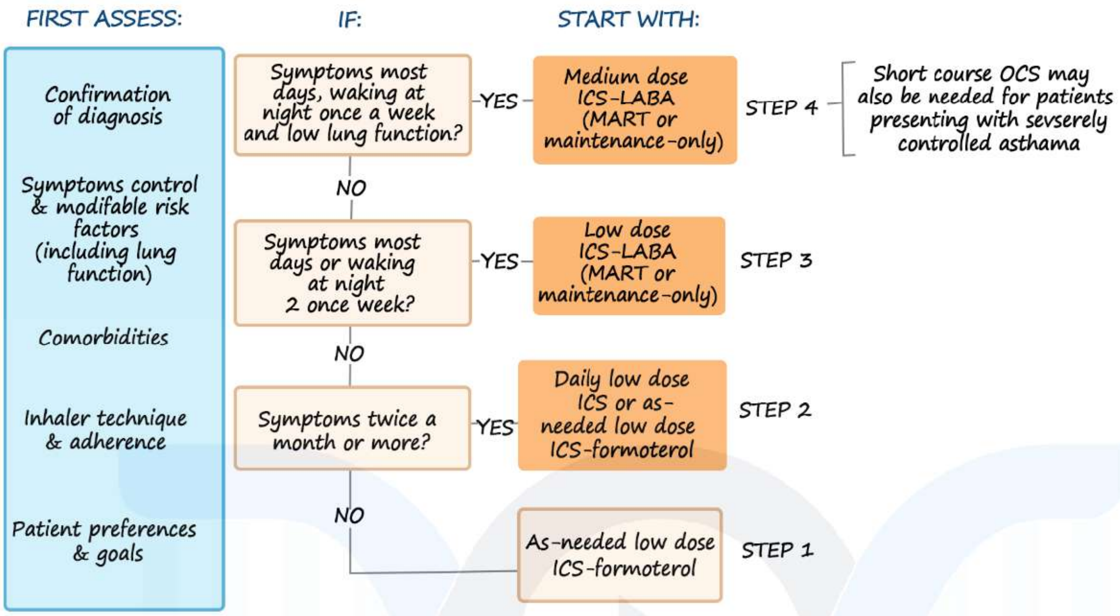
Suggested initial controller treatment in adults and adolescents with a diagnosis of asthma



Terminologies 01:38:38

1.Uncontrolled

- Individual is having frequent flareups/exacerbation

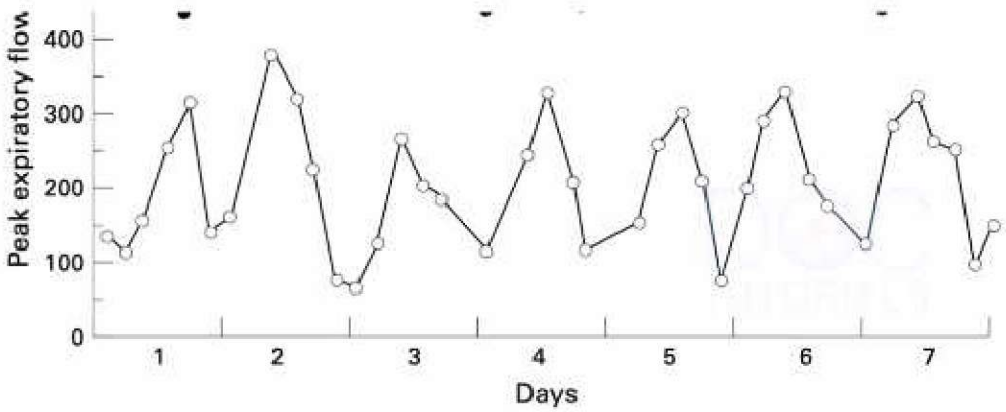
2.Difficult to treatment asthma

- Individual is having frequent flareups/exacerbation in spite of preventive therapy
- Contributory factors
  - Wrong diagnosis
  - Poor adherence
  - Poor technique of using MDI
  - Co-morbidities

3.Severe asthma

- Frequent flareups in spite of best optimized treatment

4.Brittle asthma



- Frequent exacerbations with lot of variability of PFT's
- Two types
  - Type 1 → oral corticosteroids
  - Type 2 → Brittle asthma

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- Exacerbations are unexpected, dramatic and severe
- Management: - S.C adrenaline

5.Exercise induced asthma

- Thermal and osmotic theory

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Waster loss evaporation
from the airway surface

Mucosal cooling
↓
Vasoconstriction
↓
Reactive hyperemia vascular engorgement
↓
±vascular leakage and oedema
→ Exercise-induced bronchoconstriction

Dehydration of ASL ± mucosa
↓
Increased (Na^{+}) (CL^{++}) (Ca^{++}) (K^{++})
↓
Increased osmolarity
↓
Cell volume changes
↓
Mediators released
↓
Smooth muscle contraction ±vascular leakage and oedema
→ Exercise-induced bronchoconstriction

- Thermal and osmotic theory

6.Aspirin sensitive asthma

- Treatment: - Inhaled corticosteroids

Management of acute exacerbation

GINA 2019 guidelines

i. Initial assessment

- A: Airway
- B: Breathing
- C: Circulation

ii. Impending respiratory failure

- Confused
- Delirium
- O/E: - Silent chest

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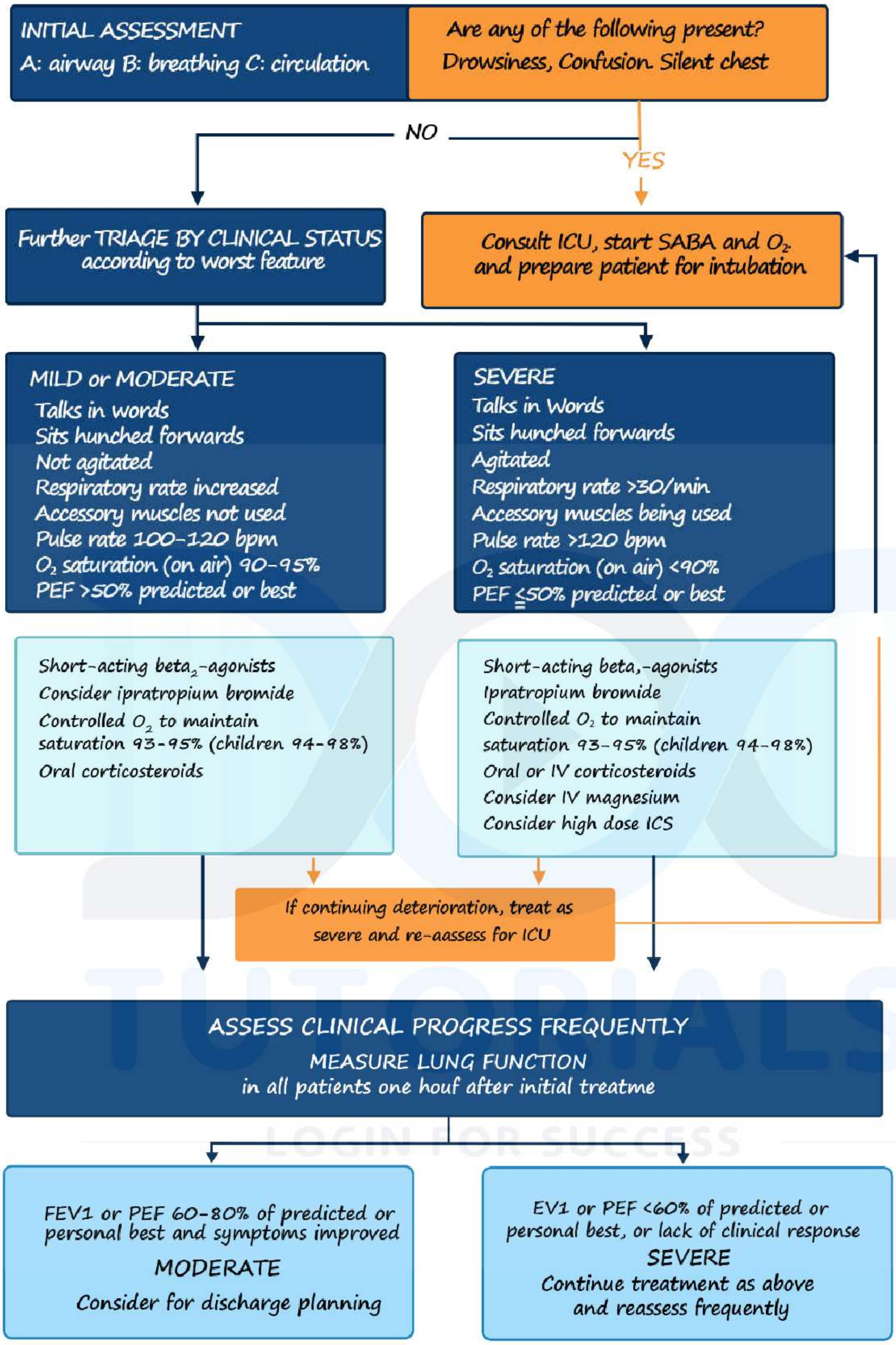

- Pulsus paradox – indicator of severe asthma
- If patient is in respiratory failure → intubate and ventilate.

COPD (CHRONIC OBSTRUCTIVE PULMONARY DISEASE)

Introduction 00:00:10

- Chronic obstructive airway disorder characterized by irreversible air flow limitation
- 3 domains
  - – emphysema
  - – chronic bronchitis
  - – small airway disease (Bronchiolitis

Emphysema 00:04:46

- Characterized by irreversible damage and dilatation of respiratory acinus

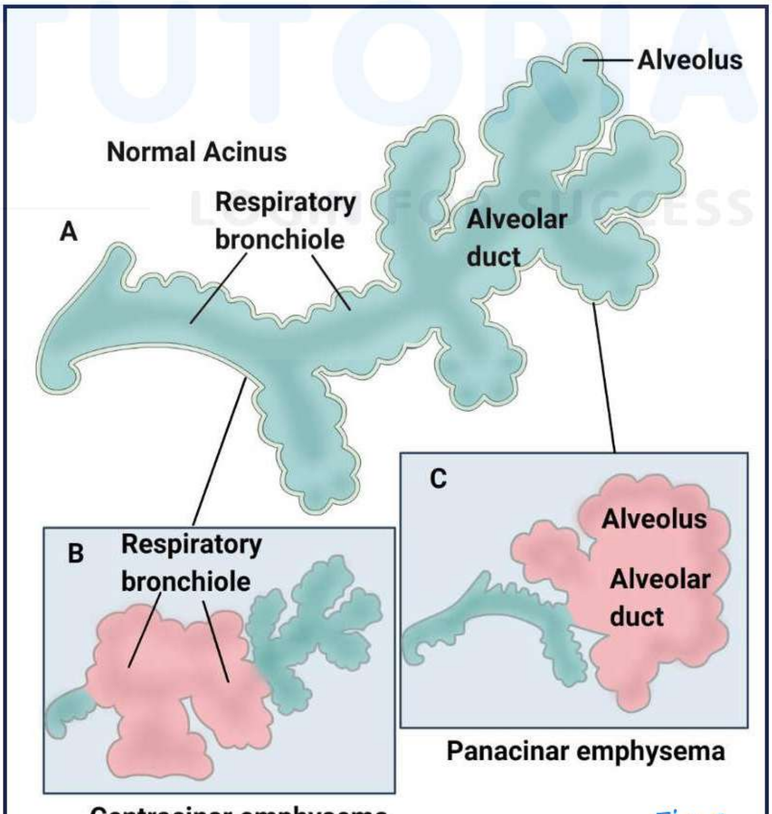

Fig: 1

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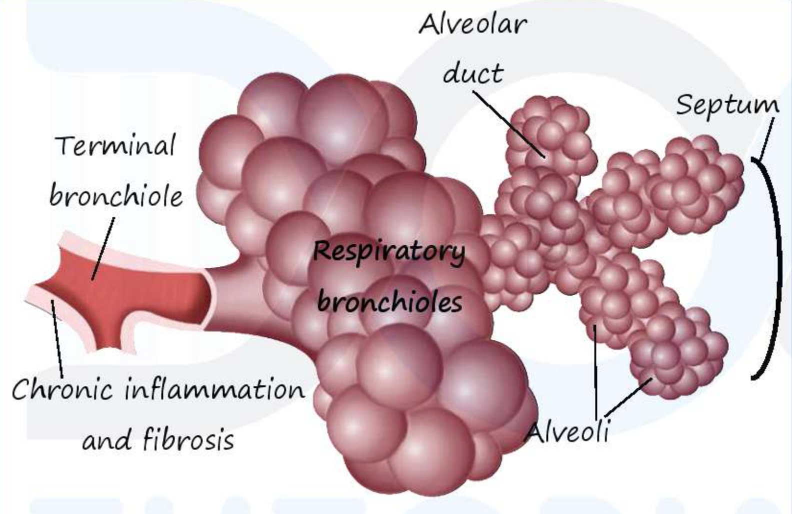
- Respiratory acinus is distal to terminal bronchiole
  - Respiratory bronchiole
  - Alveolar duct
  - Alveolus

Patterns Of Emphysema

- centriacinar/centrilobular pattern (Most common pattern) (most common in upper lobe)



Centrilobular emphysema Fig: 2

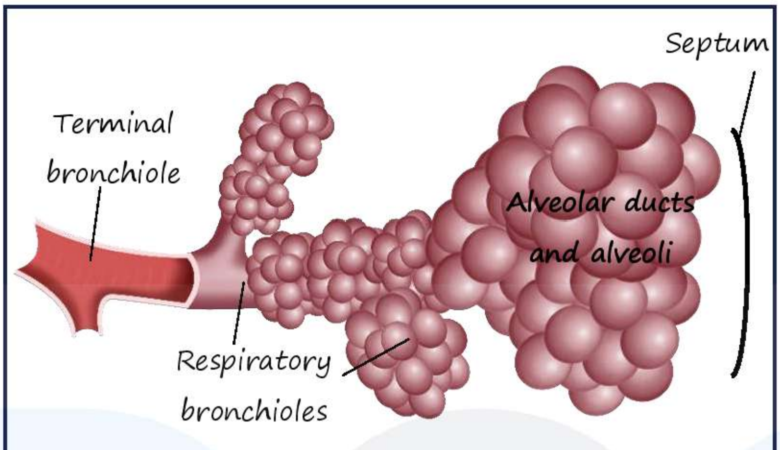
Centrilobular emphysema
↓
Brunt of attack accurses in respiratory bronchioles
↓
Respiratory bronchioles dilated
↓
Blebs

- In centriacinar emphysema, proximal part of respiratory acinus involved
- Most common pattern among smokers – centiradian

- Paraseptal emphysema

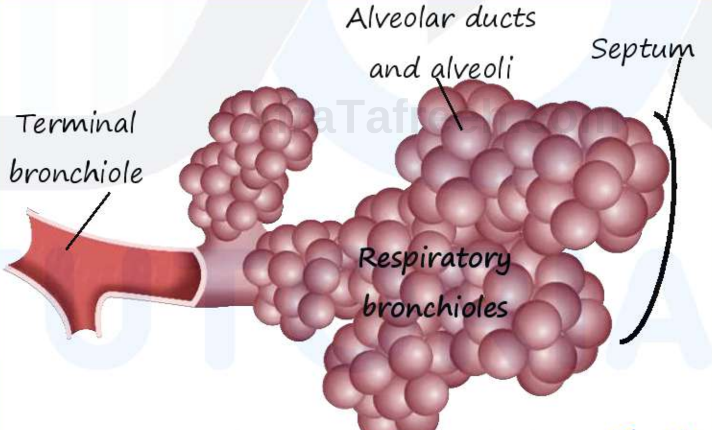
↓

distal portion of respiratory acinus involved



Paraseptal emphysema Fig: 3

- pan acinar emphysema



Panacinar emphysema Fig: 4

- irregular emphysema

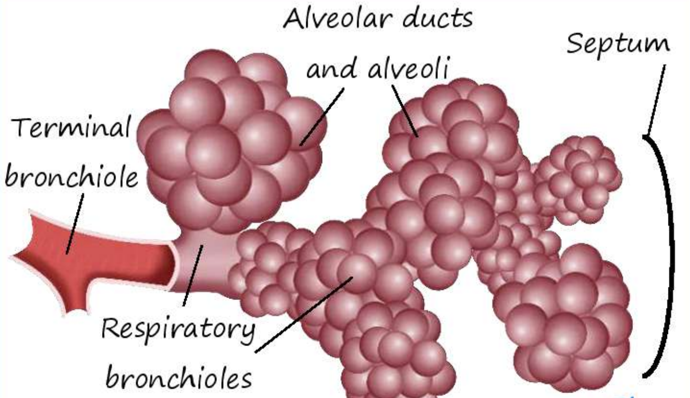


Fig: 5 Irregular emphysema

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why?

- important contributing factor – smoking
- genetic predisposition
- chronic inflammation + → cells involved are
  - – macrophages
  - – neutrophils
  - – lymphocytes
- protease – antiprotease balance is maintained
- if elastase action is unopposed → destruction of walls of airway
- it is important to maintain good oxidant-antioxidant

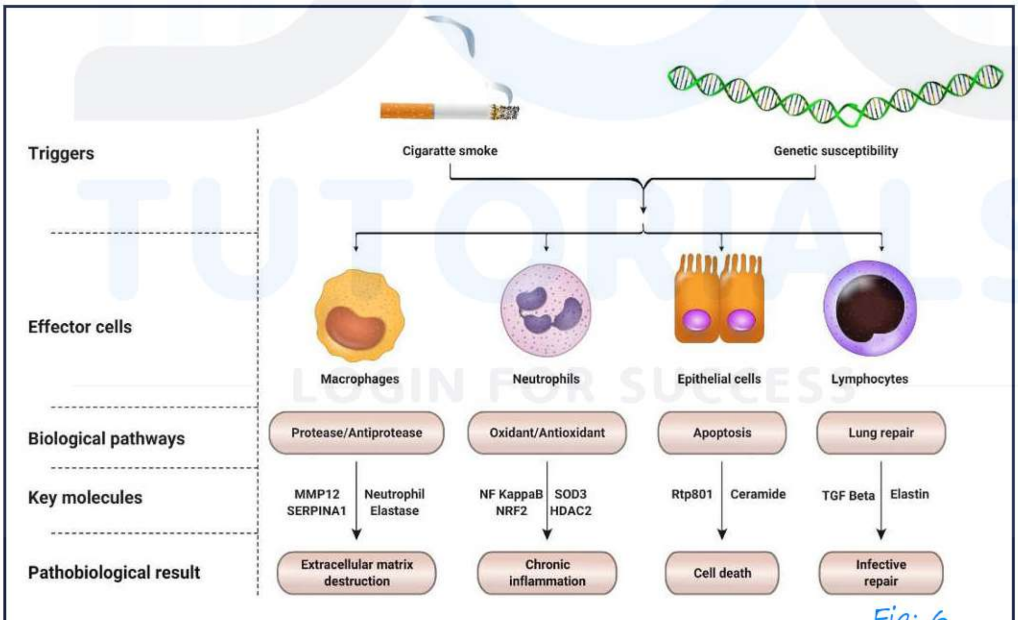

Fig: 6

Gas exchange abnormalities 00:20:18

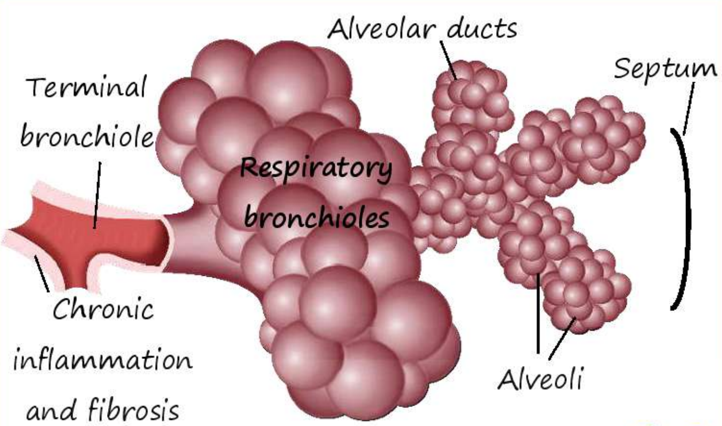

Fig: 7

- Blebs in respiratory bronchiole

  ↓

  Air trapping in respiratory bronchiole

  ↓

  Decrease pa o2 (hypoxia)

  Decrease pa co2 (hyperventilation

  Respiratory alkalosis

  Type i respiratory failure

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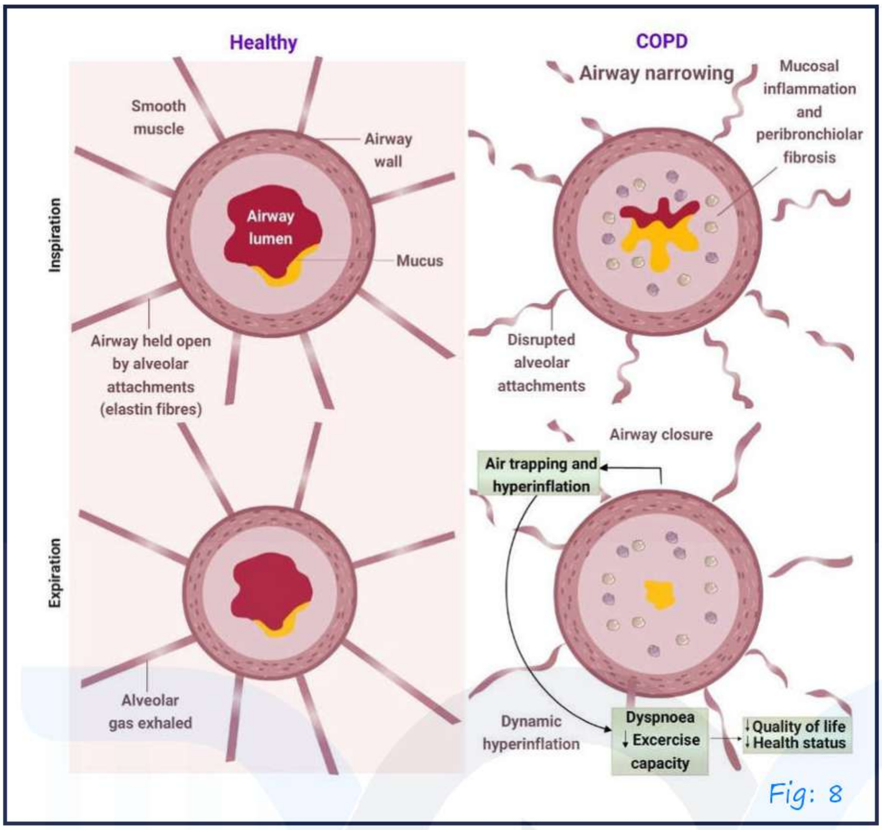

Fig: 8

- Hypoxia → pulmonary vasoconstriction

↓

Pulmonary hypertension

↓

Cor pulmonale

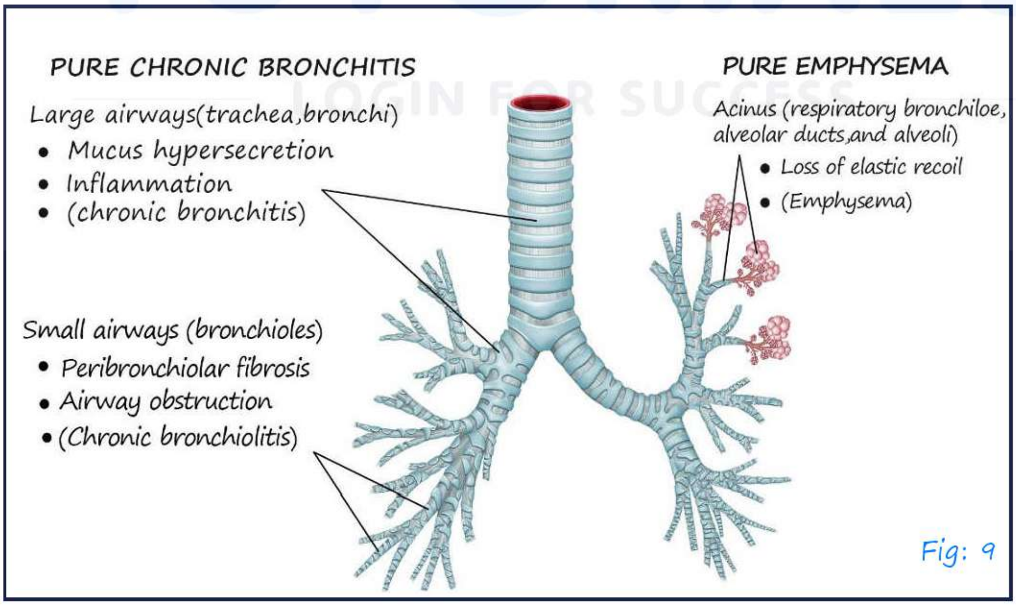

Fig: 9

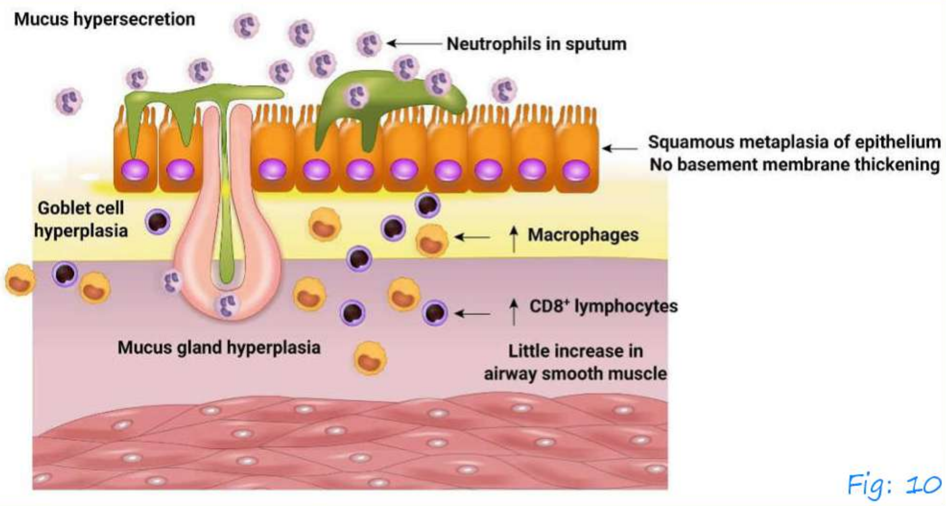

Fig: 10

- There occurs
  - Goblet cell hyperplasia
  - Squamous metaplasia
- Mucous plugs in inflamed airways – chronic bronchitis

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Gas exchange abnormalities in chronic bronchitis

- decrease Pa O2 (Hypoxia)
- increase Pa (Co2 narcosis)
- respiratory acidosis
- pulmonary vasoconstriction

  ↓

  pulmonary HTN

  ↓

  cor pulmonale
- type I respiratory failure

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	Bronchitis	Emphysema
Age, years	40-45	50-75
Dyspnea	Mild; late	Severe; early
Cough	Early; copious sputum	Late; scanty sputum
Infections	Common	Occasional
Respiratory insufficiency	Early, periodic	End-stage
Cor pulmonale	Common	Uncommon, end-stage
Airway resistance	Increased	Normal or slightly increased

Chronic bronchitis 00:30:34

- chronic cough > 3 months for 2 consecutive years
- Hyperinflated chest tubular heart flattened dome of diaphragm

Fig: 11

Fig: 12

- Pink puffer – emphysema
  - Lean individual
  - Barrel shaped chest
- Bule bloater – chronic bronchitis
  - Obese individual
  - Cyanotic look
- O/E: - clubbing not a feature of COPD pursed lip breathing → attempt to increase intra-alveolar pressure
  - Tripod position
  - Barrel shaped chest
  - B/L wheeze

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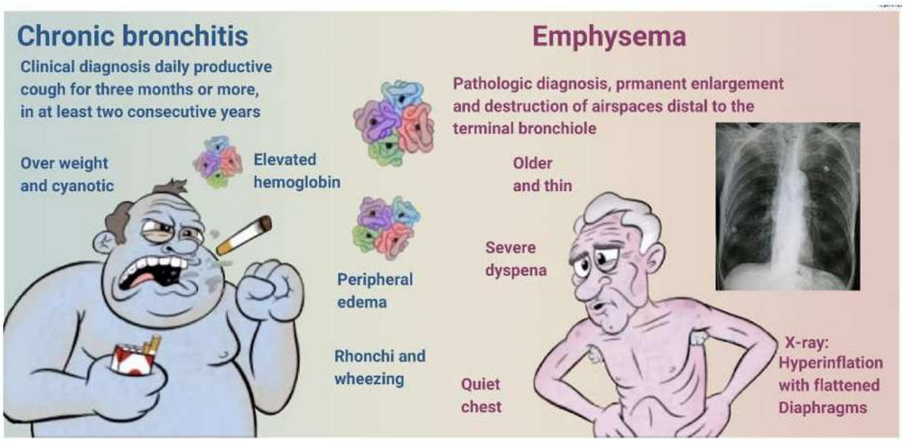

Fig: 13

– Centriacinar emphysema

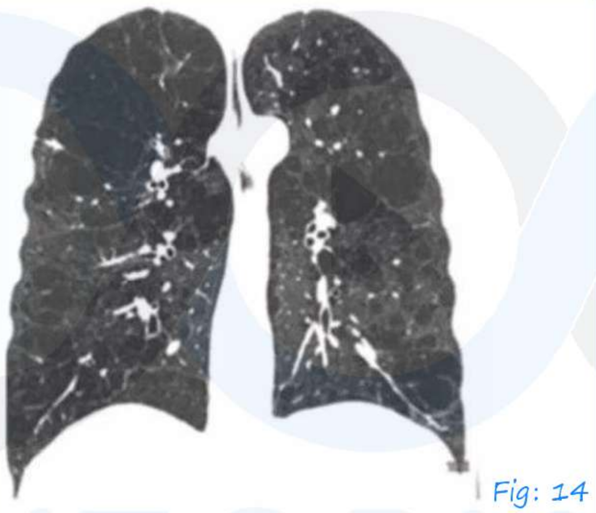
Fig: 14

- IOC: – CT Chest
- Spirometry: – FEV1/FVC < 0.7

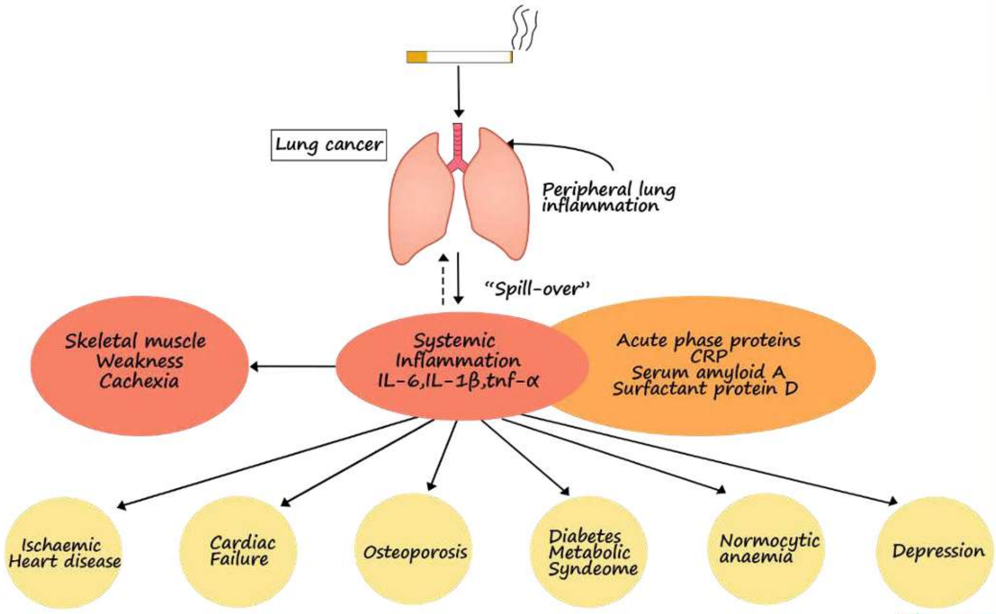

Fig: 15

Treatment of COPD 00:58:22

- 2019 – Gold guidelines (Global initiative for obstructive lung diseases)

Fig: 16

- Goals for treatment of stable COPD
  - Relieve symptoms
  - Improve exercise tolerance
  - Improve health status

  } Reduce symptoms

  And

  - Prevent disease progression
  - Prevent and treat exacerbations
  - Reduce mortality

  } Reduce risk

CLASSIFICATION OF AIRFLOW LIMITATION SEVERITY IN COPD (BASED ON POST-BRONCHODILATOR FEV_1)		
In patients with FEV1/FVC < 0.70:		
GOLD 1:	Mild	FEV, 280% predicted
GOLD 2:	Moderate	50% ≤ FEV_1 < 80% predicted
GOLD 3:	Severe	30% FEV <50% predicted
GOLD 4:	Very Severe	FEV, <30% predicted

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For symptom assessment → 2 tools

- MMRC ①②
- CAT

MODIFIED MRC DYSPNEA SCALE		
PLEASE TICK IN THE BOX THAT APPLIES TO YOU | ONE BOX ONLY | Grades 0-4		
mMRC Grade 0.	I only get breathless with strenuous exercise.	☐
mMRC Grade 1.	I get short of breath when hurrying on the level or walking up a slight hill.	☐
mMRC Grade 2.	I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.	☐
mMRC Grade 3.	I stop for breath after walking about 100 meters or after a few minutes on the level.	☐
mMRC Grade 4.	I am too breathless to leave the house or I am breathless when dressing or undressing.	☐

DOC TUTORIALS LOOK FOR SUCCESS

CATTM ASSESSMENT

For each item below, place a mark (x) in the box that best describes you currently Be sure to only select one response for each question.

EXAMPLE: I am very happy	⓪①②③④⑤	I am very sad	Score
I never cough	⓪①②③④⑤	I cough all the time	
I have no phlegm (mucus) in my chest at all	⓪①②③④⑤	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	⓪①②③④⑤	My chest feels very tight	
When I walk up a hill or one flight of stairs, I am not breathless	⓪①②③④⑤	When I walk up a hill or one flight of stairs, I am very breathless	
I am not limited doing any activities at home	⓪①②③④⑤	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	⓪①②③④⑤	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	⓪①②③④⑤	A don't sleep soundly because of my lung condition	

Exacerbation history

COPD Severity Group

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≥2 Or ≥1 with hospital admission	C Low symptoms, High risk	D high symptoms, High risk
0 or 1 (Without hospital admission)	A Low symptoms, Low risk	B high symptoms, low risk
	Mmrc 0-1 Or CAT <10	Mmrc ≥1 Or CAT ≥10
	symptoms	

INITIAL PHARMACOLOGICAL TREATMENT		
22 moderate exacerbations or 21 leading to hospitalization	Group C LAMA	Group D LAMA or LAMA + LABA" or ICS + LABA "Consider if highly symptomatic (e.g., CAT > 20) **Consider if eos 2: 300
0 or 1 moderate exacerbations (Not leading to hospital admission)	Group A A Bronchodilator	Group B A Long-Acting Bronchodilator (LABA or LAMA)
	mMRC 0-1, CAT < 10	mMRC 22, CAT > 10

- Isolated use of inhaled corticosteroids is not advised
  - LABA – Formoterol
  - LAMA – tiotropium
- Group D
  - LAMA + LABA → CAT > 20
  - LABA + ICS → Eosinophil > 300

Other treatment options

- Long term O2 therapy (LTOT)
- Lung volume reduction surgery
- Smoking cessation
  - Varenicline
  - Nicotine patches.

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TUBERCULOSIS

Introduction 00:00:12

- Caused by M. Tuberculosis
  - Obligate aerobe
  - Weak gram-positive bacillus
  - Rod shaped
  - Contains mycolic acid in cell wall → acid fast
- World TB Day – March 24th
- March 24 1882 – Robert Koch discovered M. Tuberculosis

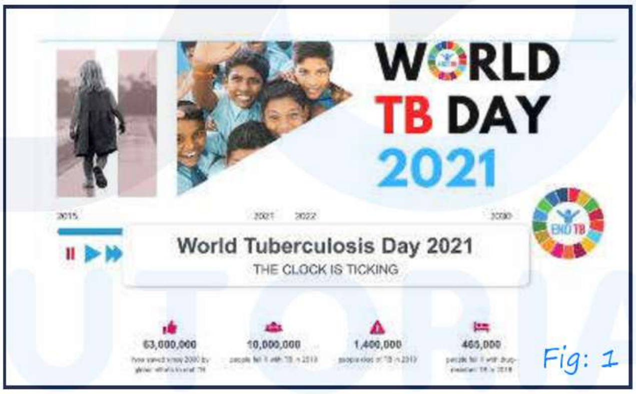
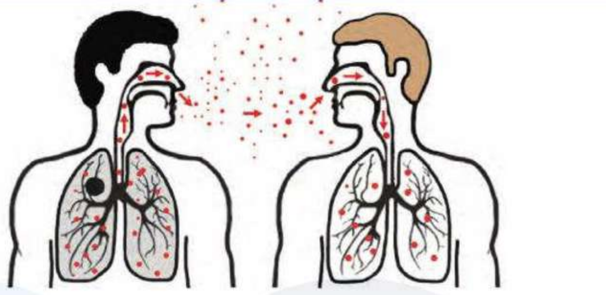


Fig: 1

Estimates of TB burden (2018)	Global (Million)	India	% of Global
Incidence TB cases	10	2.69 million	27%
Mortality of TB	1.2	440,000	31%
Incidence HIV TB	0.86	92,000	9%
Mortality of HIV-TB	0.25	9,700	4%
MDR-TB	0.5	130,000	24%
Children with TB	1.12	342,000	31%

RNTCP (Revised National Tuberculosis Control Program) 00:09:14

- Current terminology → NTEP (National Tuberculosis Elimination Programme)



Airbone transmission by Droplets Fig: 2

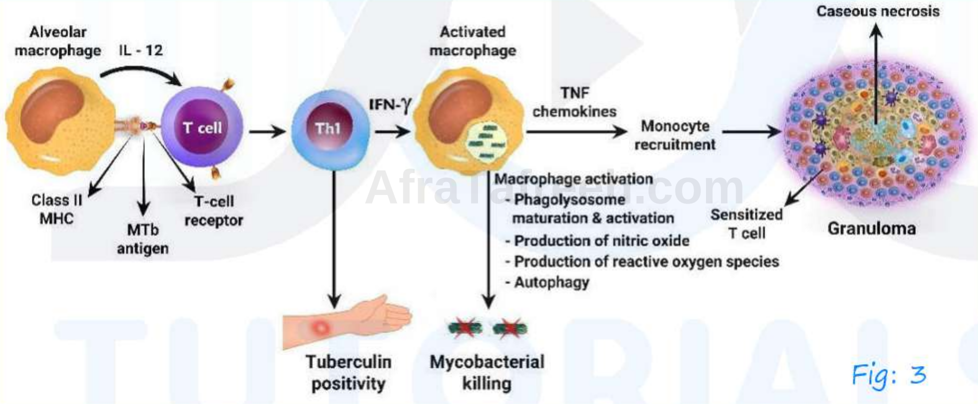


Fig: 3

- Major line of defense – Alveolar macrophages

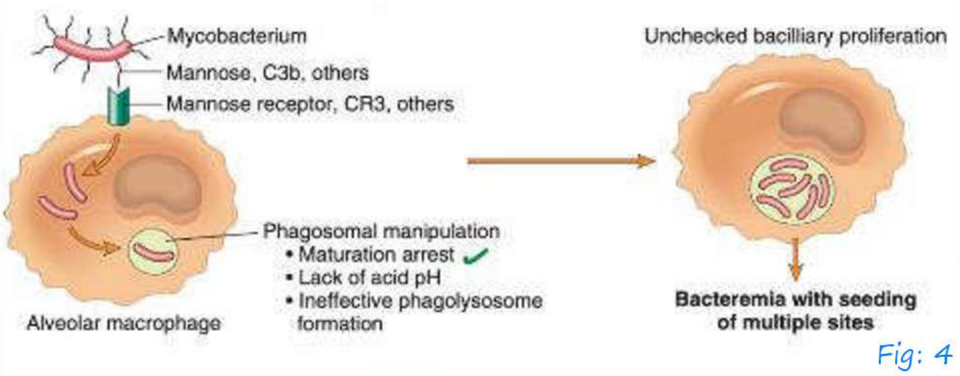


Fig: 4

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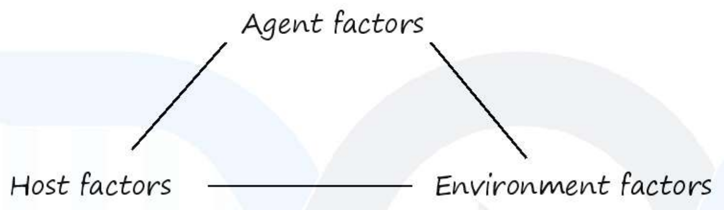
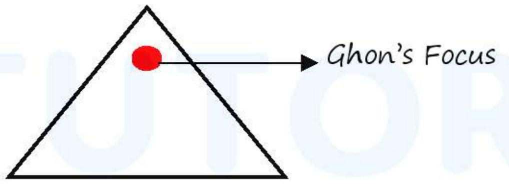
- Contributary factors
  - DM
  - HIV
  - Malnutrition
  - Alcoholic
  - CKD
  - SLE
- In TB →



Time course

- Bacilli which have been inhaled forms a focus known Ghon's focus.



- Ghon's foci is formed over lower part of upper lobe (or) upper part of middle lobe (subpleural)
- Ghon's focus ⊕ → lymphatics draining that area would be involved

  ↓

  Hilar + paratracheal lymphadenopathy
- Ghon complex → Ghon's focus _ lymphadenopathy
- Ranke complex → healed ghon focus + calcified lymph nodes

Primary TB 00:24:52

- Naïve individual developing TB infection.
- Ghon complex ⊕
- Asymptomatic
- May also have symptoms → Fever
  Pleuritis
  Erythema Nodosum
  Phlyctenular conjunctivitis

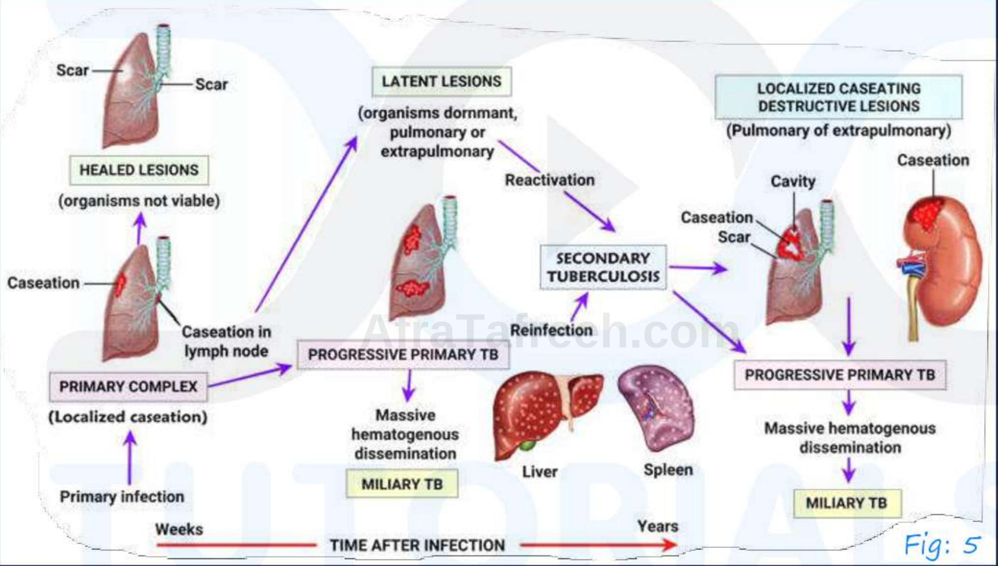
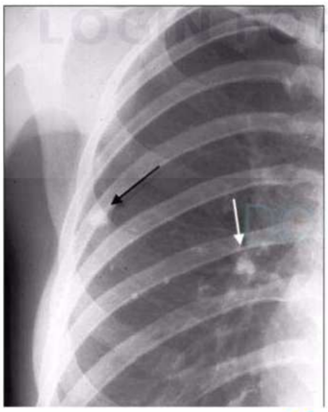


Fig: 5


Calcified hilar LN Fig: 6

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Other fates of 1° TB

1.Heated lesions

2.Progressive primary tuberculosis → occurs in decreased cell mediated immunity

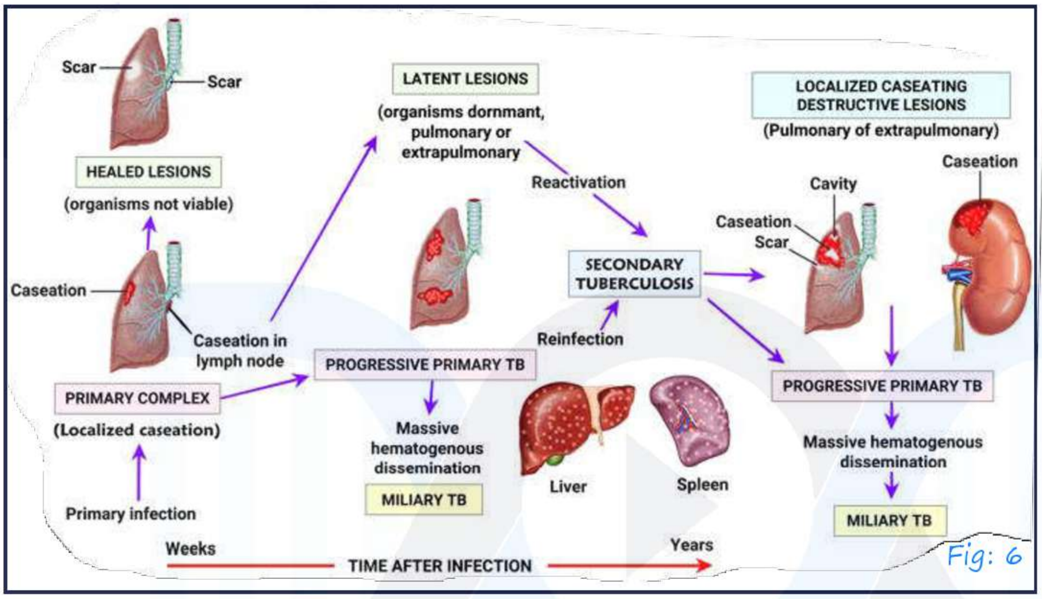
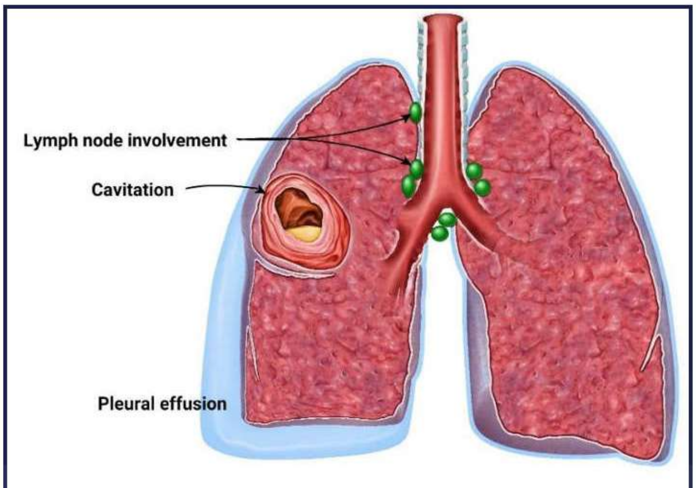


Fig: 6

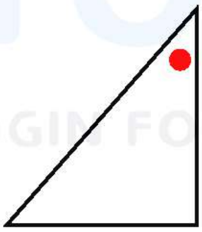
- Fever
- Pneumonia
- Enlarged LN → airway obstruction
  - Partial → Ball valve mechanism → Hyperinflation
  - Complete → Atelectasis/segmental collapse
- Cavitation
- Pleural effusion



Progressive 1° TB Fig: 7

3.Latent Tuberculosis Infection (LTBI)

- An individual can develop reactivation subsequently resulting in post primary TB/secondary TB
- Apical & posterior segment of upper lobe are involved in post 1° TB → V/Q is ratio is highest at apex of lungs



- Cavitations develop
- Symptoms → Fever
  Cough
  Loss of appetite
  Loss of weight
  Hemolysis

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Pulmonary an aneurysm adjacent to the cavitations → RASMUSSEN ANEURYSM

Night sweats

Disseminated TB

- O/E – Clubbing

  Emaciated

  Amphoric breathing

  Post tussive suction

Extra pulmonary TB 00:42:26

- Most common – Lymph node
- Pleura
- Genitourinary

  HIV + TB co-infection

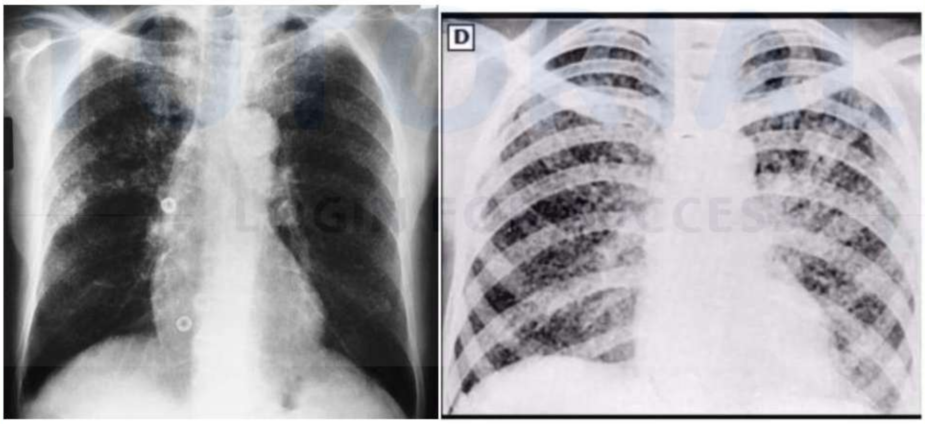

Fig: 8

- Classical military TB

  ↓

  On fundus examination – choroidal tubercles seen

Diagnosis 00:46:56

1.Sputum smear microscopy

↓

Ziehl Neelsen staining → oil immersion microscopy

sputum – NTEP

2 samples

Early morning sample | Spot sample

Either of them should be positive

- Ideally 5ml of sputum needed

Fig: 9

- Inducible sputum → Nebulization with hypertonic saline
- Bronchoscopy and bronchoalveolar lavage

Fig: 10

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- Gastric lavage in children –

Fig: 11

If the slide has:	No. of fields to be examined	Grading	Result
No AFB in 100 oil immersion fields	100	0	Negative
1–9 AFB per 100 oil immersion fields	100	Scanty	Positive
10–99 AFB per 100 oil immersion fields	100	1+	Positive
1–10 AFB per oil immersion field	50	2+	Positive
More than 10 AFB per oil immersion field	20	3+	Positive

Fluorescent AFB staining

- Primary stain in fluorescent
  - CDC recommends fluorochrome staining for detecting AFB in primary patient specimens
  - Auramine – O, Auramine Rhodamine

Read at lower magnification, less fields examined (e.g., 30 fields at 200X)

- Faster screening of smears than with ZN
- ~10% more sensitive than ZN
- Does not require use of oil immersion.

2.Culture

- LJ medium → 6-8 weeks
- Middle brook's

- Automated culture methods
  - BACTEC 460 (radiometric method)
  - BACTEC MGIT 960

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Fig: 12

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3.CB NAAT (Cartridge based Nucleic acid amplification test)

(WHO)

- Can be done in sputum
  Pleural fluid
  CSF
- Not done in urine
  blood

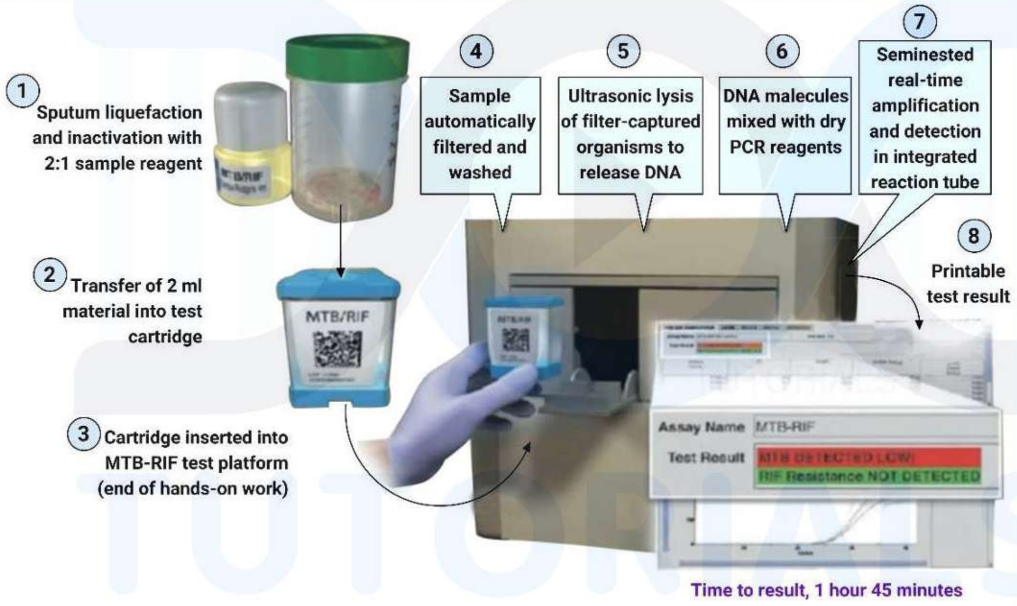

Fig: 13

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- MTB rif method: Rimfampicin resistance also detected
- Using culture as the reference standard, the pooled sensitivity of Xpert MTB/RIF in lymph node tissues or aspirates was 84.9% (95% confidence interval [CI], 72.1–92.4%) (14 studies, 849 samples); the pooled sensitivity in gastric fluid was 83.8% (95% CI, 65.9–93.2%) (12 studies, 1258 samples); and in

other tissue specimens it was 81.2% (95% C, 67.7–89.9%) (12 studies, 699 specimens). In CSF, the pooled sensitivity of Xpert MTB/RIF compared against culture as a reference standard was 79.5% (95% CI, 62.0–90.2%) (16 studies, 709 specimens); compared against a CRS it was 55.5% (95% CI: 44.2–66.3%) (6 studies, 512 specimens). In pleural fluid, the pooled sensitivity of Xpert MTB/RIF compared against culture was 43.7% (95% CI, 24.8–64.7%) (17 studies, 1385 specimens); a pooled sensitivity against a CRS was 17.0% (95% CI, 7.5–34.2%) (7 studies, 698 specimens). The pooled specificity was always greater than 98.7% if Xpert MTB/RIF was tested against a CRS. The data for other types of specimens (such as ascitic fluid, pericardial fluid, urine, blood and stool) were limited and therefore were not considered for analysis by subgroup.

Fig: 14

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4.Line probe assay (LPA)

- PCR based assay

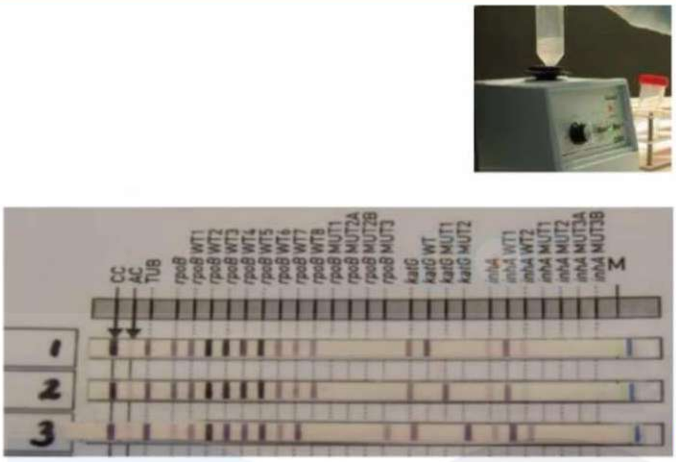

Fig: 15

- Done only when sputum smear is positive

5.Urine LAM test

- Diagnosing tuberculosis with urine lipoarabinomannan: systematic review and meta-analysis
- J. Minion, E. Leung", E. Talbot, K. Dheda', M. Pai and D. Menzies***
- ABSTRACT: Lipoarabinomannan (LAM) is a potential marker of active tuberculosis (TB). We performed a systematic review and meta-analysis regarding use of urinary LAM assays for diagnosing active TB.
- We systematically searched for published and unpublished studies that evaluated urinary LAM for active TB diagnosis. Extracted data were pooled using bivariate random effects models and hierarchical summary receiver operating

characteristic curves. Heterogeneity was explored through subgroup analysis and meta-regression. Quality was assessed according to standardized QUADAS (Quality Assessment of Diagnostic Accuracy Studies) criteria.

- In seven studies that assessed test accuracy in microbiologically confirmed cases only, estimates of sensitivity ranged from 13% to 93%, while specificity ranged from 87% to 99%. In five studies that assessed accuracy in clinical and confirmed TB cases, sensitivity ranged from 8% to 80%, while specificity ranged from 88% to 99%. In five studies with results stratified by HIV status, sensitivity was 3-53% higher in HIV-positive than HIV-negative subgroups; sensitivity was highest with advanced immunosuppression.
- The LAM urinary assay has several characteristics that make it attractive for diagnosing active TB, but has suboptimal sensitivity for routine clinical use. Further studies are needed to evaluate the potential value of the LAM assay in individuals with advanced HIV or for diagnosis of pediatric TB.

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6.To detect TB infection

Mantoux tuberculin skin test

Quantiferon – TB gold in-tube test (QFT-GIT)

T-spot. TB test

- Mantoux tuberculin skin test
- Interferon gamma release assay
  - QuantiFERON TB gold In-Tube test (QFT-GIT)
  - TB spot, TB test

- Cannot distinguish between disease and infection

Fig: 16

- Mantoux test

↓

0.1 ml (5TU) of PPD RT – 23 (purified protein derivative)

↓

Injected intradermally on the volar aspect of forearm

↓

48-72 hours later

↓

Width of induration noted

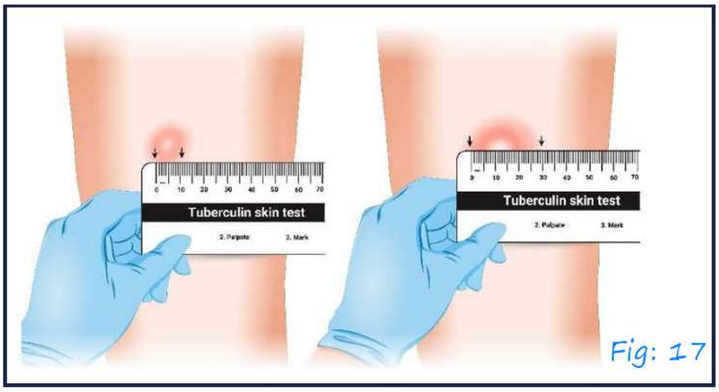

Fig: 17

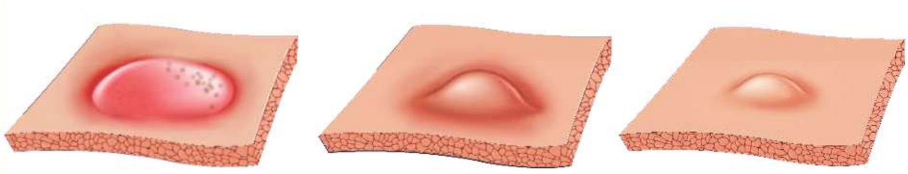
Fig: 18

IGRA

- Based on serum sample

TST	IGRA
Tuberculin is injected under the skin and produces a delayed-type hypersensitivity reaction if the person has been infected with M. tuberculosis	Blood is drawn for testing; test measures the immune response to the TB bacteria in whole blood
Requires two or more patient visits to conduct the test	Requires one patient visit to conduct the test
Results are available 48 to 72 hours later	Results can be available in 24 hours (depending on the batching of specimens by the laboratory and transport)
Can cause booster phenomenon	Does not cause booster phenomenon
Reading by HCW may be subjective	Laboratory test not affected by HCW perception or bias
BCG vaccination can cause false positive result	BCG vaccination does not cause false positive result and infection with most nontuberculous mycobacteria does not cause false-positive result
A negative reaction to the test does not exclude the diagnosis of LTBI or TB disease	A negative reaction to the test does not exclude the diagnosis of LTBI or TB disease

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7.Chest X-ray

8.CT thorax - Abdomen

9.CB NAAT from – Lymph node aspirate

- Pleural fluid
- CSF
- Pericardial fluid
- Ascitic fluid

→ Extrapulmonary cases

Treatment of TB 01:17:10

- NTEP – National Tuberculosis Elimination Programme
- Previously RNTCP

NTEP guidelines 2020

Fig: 19

- Lateral flow urine lipoarabinomannan (LF-LAM) assay can only be used for diagnosis of TB in HIV positive patients with signs and symptoms of TB (pulmonary and/or extra-pulmonary) who have a CD4 cell count less than or equal to 100 cells/μL.

- C-Tb is the next generation skin test for detection of tuberculosis. It has high specificity and contains the same antigens used in IGRA i.e., ESTA 6 and CFP 10. It is unaffected by BCG vaccination status and hence can be used as a tool for latent TB diagnosis.
- C.TB – ESAT – 6, CFP-10

Treatment
- Drug sensitive TB
- Drug resistant TB

- Investigation for drug resistance
  ↓
  - CB NAAT – Rifampicin
  - Line probe assay – Rifampicin & INH (1st line)
    2nd line assay ⊕

Methods for drug susceptibility testing

I. Rapid molecular drug resistance Testing (DRT) – Genotype
   a. Nucleic acid amplification test (NAAT)
      i. Cartridge based Gene-Xpert platform,
      ii. Chip based TruNAAT platform
   b. Line Probe Assay (LPA)
      i. First line (H&R)
      ii. Second line (Lfx, Mfx, Km, Cm, Am)

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II. Growth-based phenotypic drug susceptibility testing (DST)

a. First line drugs: R, H, E, Z

b. Second line drugs: S, Lfx, Mfx, Km, Cm, Am

c. Other drugs: Lzd, Cfz, Bdq, Dlm PAS etc.

- UDST – Universal drug sensitivity testing

↓

If possible, do CB-NAAT for everyone.

Drug sensitive TB

6 months

Intensive phase → 2 months → HRZE

Continuous phase → 4 months → HRE

- H – INH
- R – Rifampicin
- Z – Pyrazinamide
- E – Ethambutol

Type of TB	Treatment Regimen in IP	Treatment regimen in CP
New and previously treated cases (H and R sensitive/unknown)	2 HRZE	4 HRE

- Drug dosages for first line anti-TB drugs

Drugs	Adult
Isoniazid	5 mg/kg daily (4 to 6 mg/kg)
Rifampicin	10 mg/kg daily (8-12 mg/kg)
Pyrazinamide	25 mg/kg daily (20-30 mg)
Ethambutol	15 mg/kg daily (12-18 mg/kg)
Streptomycin	15 mg/kg daily (15-20 mg/kg)

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- Daily fixed dose regimen
- Periodically monitor the patient

Classification based on drug resistance

a. Mono-resistance (MR): A TB patient, whose biological specimen is resistant to one first-line anti-TB drug only.

b. Poly-Drug Resistance (PDR): A TB patient, whose biological specimen is resistant to more than one first-line anti-TB drug, other than both isoniazid (INH) and Rifampicin (R).

c. Multi Drug Resistance (MDR): A TB patient, whose biological specimen is resistant to both isoniazid and

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rifampicin, with or without resistance to other first line drugs, based on the results from a quality assured laboratory.

d. Rifampicin Resistance (RR): resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs excluding INH. Patients, who have any Rifampicin resistance, should also be managed as if they are an MDR TB case.

e. Extensive Drug Resistance (XDR): A MDR TB case whose biological specimen is additionally resistant to a fluoroquinolone (ofloxacin, levofloxacin, or moxifloxacin) and a second-line injectable anti TB drug (kanamycin, amikacin, or capreomycin) from a quality assured laboratory.

Drug resistant

INH monoresistance	MDR TB
(or)	(or)
Polydrug resistance	Rifampicin resistance

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Regimen	Intensive phase	Continuation phase	Total duration
All oral H mono/poly DR TB regimen			6 months Lfx, R, Z, E
Shorter MDR TB/RR TB regimen	4-6 months Mfx^h, Km/Am, Eto, Cfz, Z, H^h, E	5 months Mfx^h, Cfz, Ze, E	9-11 months
All oral longer MDR TB			18-20 months Bdq (6), Lfx, Lzd, Cfz, Cs

- Mfx^h – Moxifloxacin high dose
- KM – Kanamycin
- AM – Amikacin
- Eto –ethionamide
- Cfz – Clofazamine
- Z – Pyrazinamide
- H^h – INH high dose
- E – Ethambutol
- Bdq – Bedquiline → first 6 months only
- Lfx – Levofloxacin
- Lzd – Line zolid
- Cs – Cyclophosphamide.

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BRONCHIECTASIS

- Bronchi – airway; ectaria – dilatation
- Abnormal & irreversible dilatation of bronchial wall

Etiopathogenesis 00:01:24

Etiopathogenesis

Focal bronchiectasis
↓
Foreign body
Tumor
Lymph node

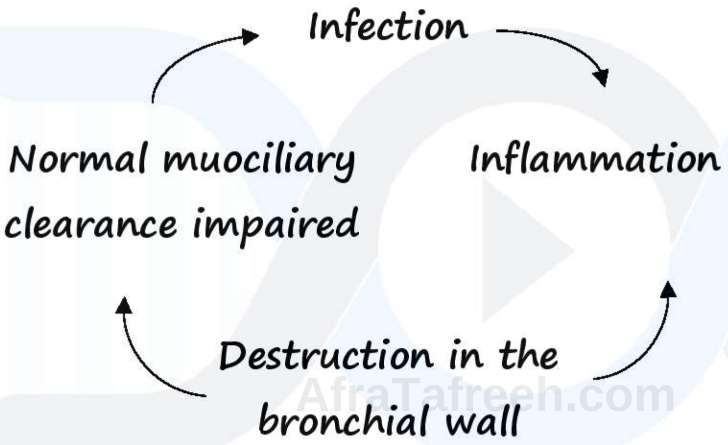
Diffuse bronchiectasis

Diffuse bronchiectasis

Infectious	**Non infectious**
↓ M.TB Pseudomonas H. influenza Mycoplasma NTM (MAC) (Mycobacterium avium)	↓ - Immune compromised ↓ Hypogamma - globulinemia HIV - Genetic causes ↓ Cystic fibrosis Kartagener's syndrome α_1 antitrypsin deficiency - Immune ↓ Rheumatoid arthritis Sjogren syndrome

	IBD ABPA ↓ HS reaction to aspergillus fumigatus Aspiration

Vicious cycle of bronchiectasis 00:08:14



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Major Etiologies of Bronchiectasis and Proposed		
Pattern of lung involvement	**Etiology by category (examples)**	**Workup**
Focal	Obstruction (aspirated foreign body, tumor mass)	Chest imaging (chest x-ray and/or chest CT); bronchoscopy
Diffuse	Infection (bacterial, nontuberculous mycobacterial)	Sputum Gram's stain/ culture: stains/cultures for acid-fast bacilli and fungi. If no

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		pathogen is identified, consider bronchoscopy with bronchoalveolar lavage.
	Immunodeficiency (hypogamma-globulinemia, HIV infection, bronchiolitis obliterans after lung transplantation)	Complete blood count with differential; immunoglobulin measurement: HIV testing
	Genetic causes (cystic fibrosis. Kartagener's syndrome, a antitrypsin deficiency)	Measurement of chloride levels in sweat (for cystic fibrosis). a antitrypsin levels; nasal or respiratory tract brush/biopsy (for dyskinetic/immotile cilia syndrome); genetic testing
	Autoimmune or rheumatologic causes (rheumatoid arthritis, sjogren's syndrome, inflammatory	Clinical examination with careful joint exam, serologic testing (e.g., for rheumatoid factor). Consider workup

	bowel disease); immune-mediated disease (allergic bronchopulmonary aspergillosis)	for allergic bronchopulmonary aspergillosis, especially in patients with refractory asthma
	Recurrent aspiration	Test of swallowing function and general neuromuscular strength
	Miscellaneous (yellow nail syndrome, traction bronchiectasis from post-radiation fibrosis or idiopathic pulmonary fibrosis)	Guided by clinical condition
	Idiopathic	Exclusion of other causes

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Types 00:12:58

- Cylindrical/tubular
- Saccular/cystic
- Varicose

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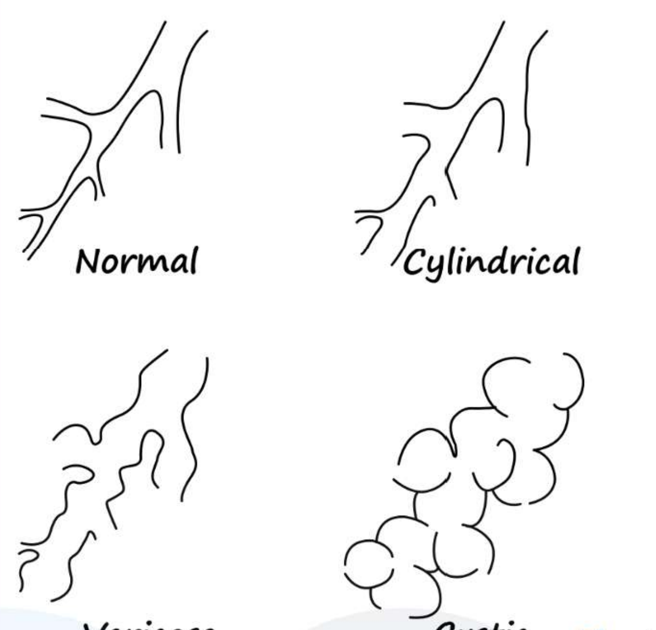

Fig: 1

Clinical features 00:14:28

- Chronic disease process
  - Production cough with foul smelling sputum (Bronchorrhea)
  - Fever
  - Systemic features – weight loss malaise
  - Hemoptysis

O/E

- Clubbing ⊕
- Bronchiectasis sicca
  - No clubbing
  - Not much foul-smelling discharge
- On auscultation → worse leathery crepitations (mid inspiration)

Complications 00:18:26

- Most – massive hemoptysis
- Amyloidosis
- Cor pulmonale

Investigations 00:19:38

- Increase TC, increase ESR, increase CRP → Acute exacerbation
- Sputum study
- Blood C & S
- CXR
- PFT → obstructive pattern traction bronchiectasis

↓

Restrictive pattern

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Tram track sign

Fig: 2

- IOC: HRCT

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Fig: 3

- Bronchiectasis involving the upper lobe
  - TB
  - Cystic fibrosis
  - Radiation fibrosis
- Lower lobe → Aspiration
- Middle lobe
  - NTM
  - ABPA

Middle lobe bronchiectasis + TB lymphadenopathy

↓

Brock's syndrome

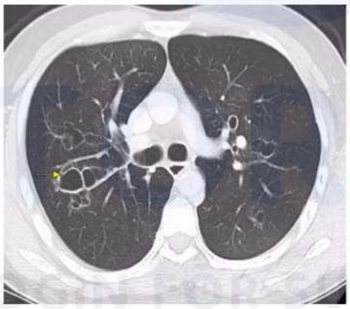
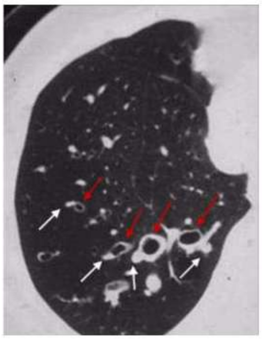


Fig: 4

Williams-Campbell syndrome – absence of cartilage



Singet ring sign Fig: 5

- Tree in bud sign

Treatment 00:28:26

i. Antibiotic therapy

ii. Bronchial hygiene

Chronic bronchial infection

Long-term inhaled (or) oral antibiotic therapy

Eradication of new pathogenic microorganisms

Antibiotics treatment of exacerbations

Structural lung disease

Long term bronchodilator therapy

Surgery

Pulmonary rehabilitation

Inflammation

Long-term anti-inflammatory therapies

Impaired mucociliary clearance

Long-term mucoactive treatments

Airway clearance

Exacerbation of bronchiectasis

↓

Treatment antibiotics → 2weeks

NTM – Macrolide + Rifampicin + ethambutol

First/new isolation of P. aeruginosa

- Consider repeat sample to confirm persistent P. aeruginosa
- Oral fluroquinolone example: ciprofloxacin 750 mg b.i.d ↓ (Initial phase 2 weeks) Intravenous antibiotics e.g., beta-lactam plus aminoglycoside ↓ Inhaled antibiotics, e.g., colistin/ tobramycin/ gentamicin ↓ Total duration 3 months
- Intravenous antibiotics, e.g., beta-lactam plus aminoglycoside ↓ (Initial phase 2 weeks) Inhaled antibiotics, e.g., colistin/ tobramycin/ gentamicin ↓ Total duration 3 months

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First/new isolation of P. aeruginosa

↓

Oral fluroquinolone OR
intravenous antibiotics plus
inhaled antibiotics, e.g.,
ciprofloxacin 750 mg b.i.d.
plus inhaled colistin

↓

(Initial phase 2 weeks)
Continued
Inhaled antibiotics

↓

Total duration
3 months

- Newly detected pseudomonas – 3 months

Bronchial hygiene

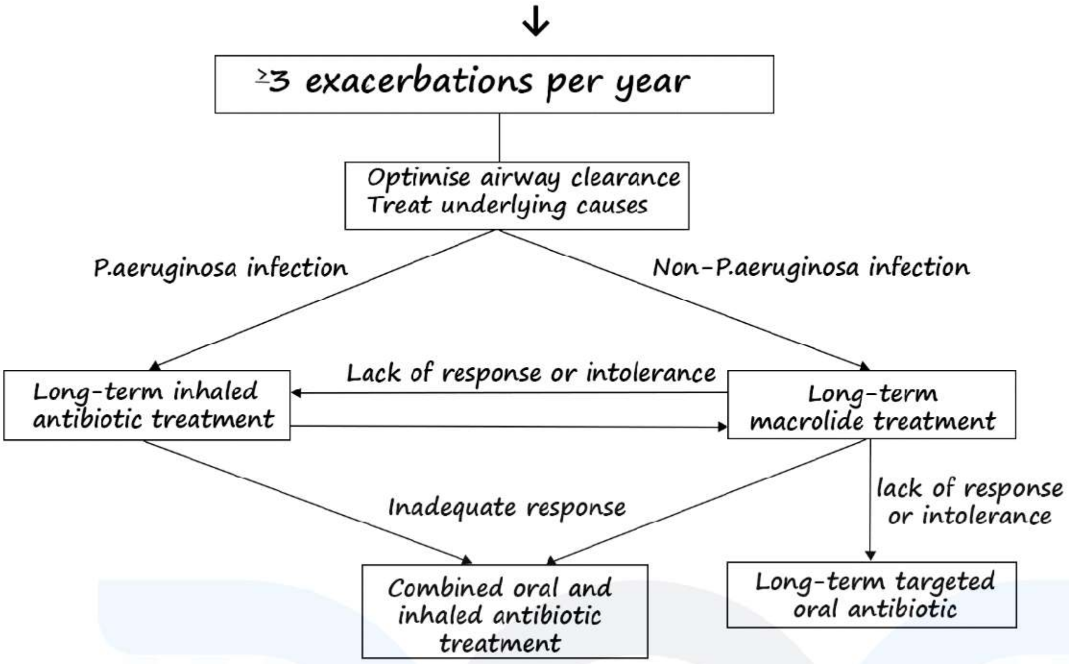
- Nebulization with hypertonic saline and bronchodilators
- Chest physiotherapy → assisted devices
- Inhaled antibiotics

Massive hemoptysis

↓

Bronchial artery embolization.

Recurrent exacerbations



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ARDS (ACUTE RESPIRATORY DISTRESS SYNDROME)

Introduction 00:00:20

- Characterized by
  - Acute onset severe dyspnea
  - Hypoxemia
  - Diffuse pulmonary infiltrates
  - Respiratory failure
- Previously called acute lung Injury

Direct	Indirect
• pneumonia	• sepsis (most common cause)
• aspiration of gastric contents	• trauma
• near drowning	• burns
• pulmonary contusion	• multiple massive blood transfusion
• toxic inhalational injury	• drug overdose
	• pancreatitis

Pathogenesis 00:02:18

3 stages:

- Exudative stage (day 1 – day 7)
- Proliferative stage (day 7 – day 21)
- Fibrotic stage (beyond 3 weeks)

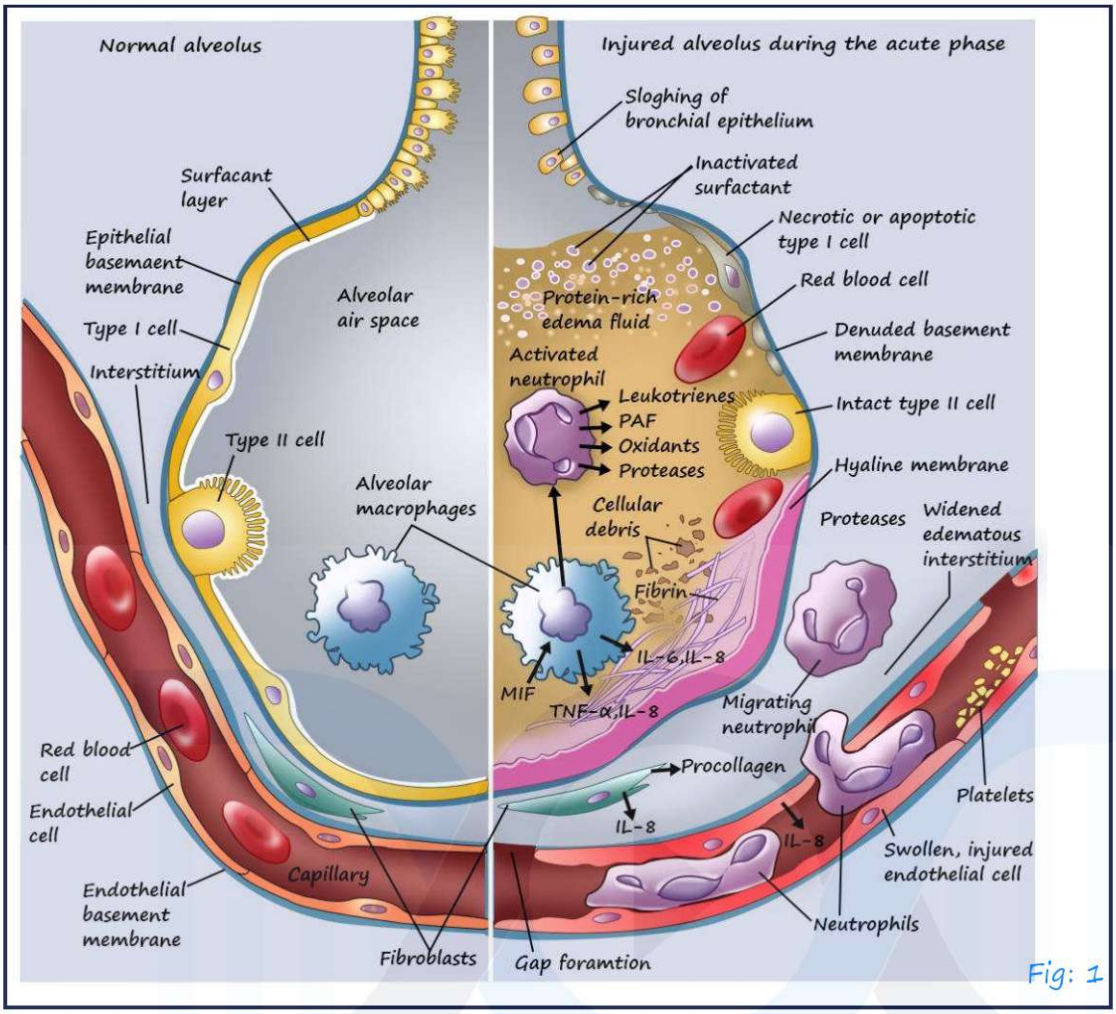

Fig: 1

1.Exudative stage

- In normal individuals → intact alveo – capillary membrane
- In ards (direct or indirect injury)

  ↓

  Alveo – capillary membrane disrupts

- Injury to – alveolar epithelial cells (Type I pneumocytes) / capillary endothelial cells.

  ↓

  Disruption of integrity of alveolo-capillary membrane

  ↓

  Alveolar and interstitial inflammation

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- Protein rich fluid
- Inflammatory cells

- Macrophages will secrete certain cytokines →
  - il -1
  - il-6
  - Il-8
  - Tnfα
  - Ltb4

  (il-1, il-6, Il-8: Further increase inflammatory cell)

- Dysfunction surfactant → predispose to alveolar collapse
- Protein accumulation in alveoli + dysfunctional surfactant

  ↓

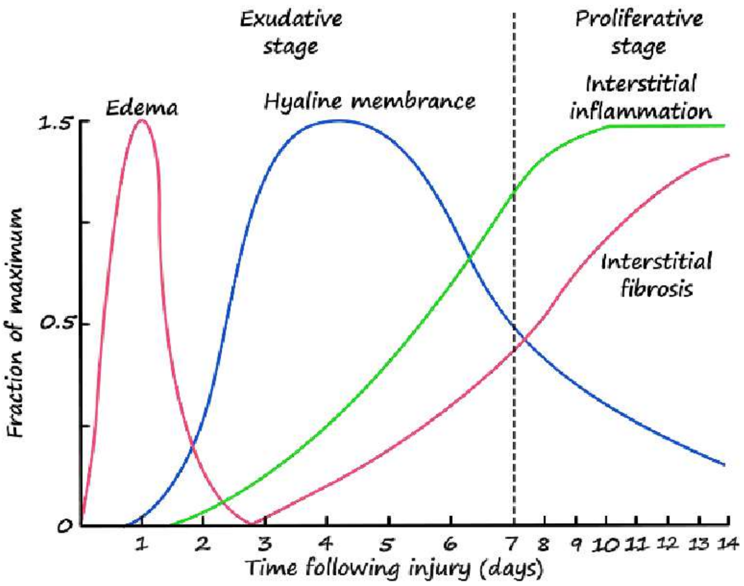
  Hyaline membrane formation

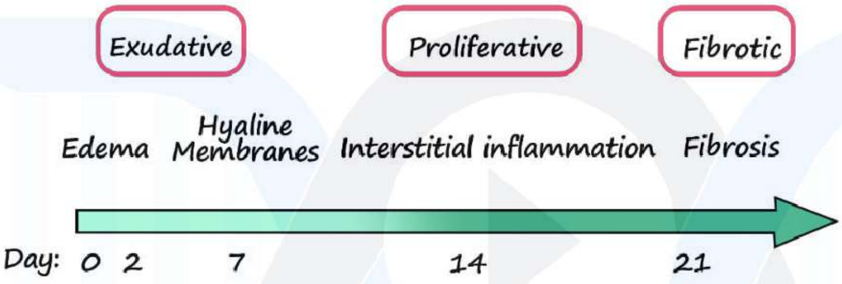
2.Proliferative stage

- Disease resolution begins
- Alveolar exudates begin to organize
- Neutrophil rich inflammatory fluid → lymphocyte rich inflammatory fluid

3.Fibrotic

- Fibroblast activation → triggers fibrosis
- Structural changes occur





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Gas exchange abnormalities

- Alveolar flooding occurs in ARDS

↓

Diffusion abnormality

↓

– Decrease pao2 (hypoxemia)

– Normal / decrease pa co2

– Respiratory alkalosis

– Increase (a-a) gradient

– Type i respiratory failure

↓

Type ii respiratory failure

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Pulmonary vasculature

- Pulmonary vasoconstriction

  ↓

  Pulmonary HTN

Diagnosis 00:26:40

- Clinical setting

  Criterial – berlin criteria

  – Mild

  – Moderate

  – Severe

Diagnostic Criteria for ARDS			
Severity: oxygenation	Onset	Chest radiograph	Absence of left atrial hypertension
Mild: 200 mmHg < Pao/Fio, $ 300 Moderate: 100 mmHg < Pac/Fa, $ 200 mmHg Severe: Pao/Fo, s 100 mmHg	Acute: Within 1 week of a clinical insult or new or worsening respiratory symptoms.	Bilateral opacities consistent with pulmonary ederra not fully explained by effusions, lobar/lung collapse, or nodules	Hydrostatic edema is not the primary cause of respiratory failure. If no ARDS risk factor is present, then some objective evaluation is required (eg, echocardiography) to rule out hydrostatic edema

"As assessed on at least 5 cm H, O of positive end expiratory pressure

(PEEP).

- <u>Pa O_2</u> ratio decreased

  Fi O_2

  – Mild: - 200-300mmhg

  – Moderate: - 100-200mmhg

  – Severe: - ,100

- Pa O_2/Fi O_2 ratio calculated when PEEP >5cm H_2O

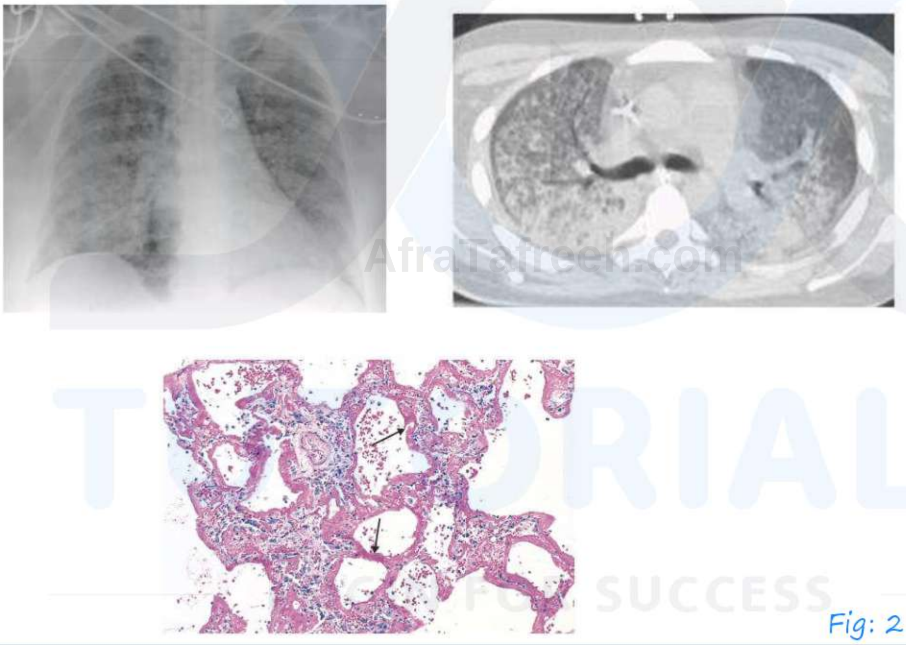

Fig: 2

Treatment: 00:37:10

- Treatment triggering cause
- Mechanical ventilation → low tidal volume ventilation (<6ml/kg)

  ↓

  High trial volume cases volutrauma

- To prevent atelectrauma

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  - Low tidal volume ventilation
  - High peep
- Inverse ratio ventilation (increase inspiration)
- High frequency ventilation
- Ecmo – extra corporeal membrane oxygenation
- Early neuromuscular blockade

Evidence-Based Recommendations for ARDS Therapies	
Treatment	**Recommendation"**
Mechanical ventilation	
Low tidal volume	A
Minimized left atrial filling	B
pressures	B[b]
High-PEEP or "open lung"	B[b]
Prone position	C
Recruitment maneuvers	D
High-frequency ventilation	
ECMO	B[b]
Early neuromuscular blockade	B[b]
Glucocorticoid treatment	D
Inhaled vasodilators (e.g., inhaled NO, inhaled epoprostenol)	C
Surfactant replacement, and other anti-inflammatory therapy (e.g., ketoconazole, PGE, NSAIDs)	D

- No role for steroids
- prone position ventilation

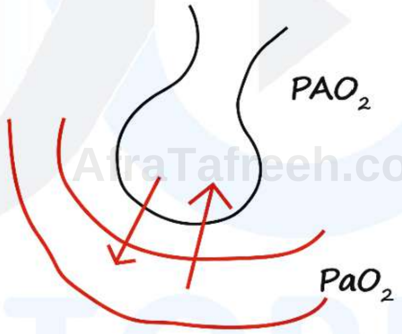
RESPIRATORY FAILURE

- 4 types
  - Type 1
  - Type 2
  - Type 3
  - Type 4

  Based on pathophysiology

Type I respiratory failure 00:01:44

- Oxygenation failure → Hypoxia without hypercarbia



- Alveolar flooding ⊕
- Impairment of normal diffusion across alveolo capillary membrane
- PaO_2 decrease → Hypoxemia
- Also referred to as hypoxia respiratory failure
- (A-a) gradient: Increased
- $PaCo_2$ → Normal/decreased

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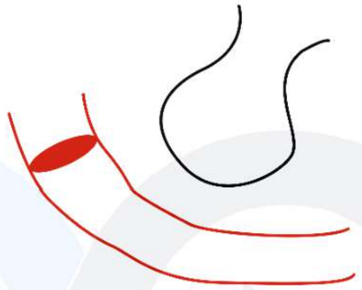
Conditions producing type I respiratory failure

- Pneumonia
- ARDS
- Congestive cardiac failure
- Interstitial lung disease
  - Pulmonary embolism – dead space ventilation



- Acute asthma

Type II respiratory failure 00:10:26

- Ventilation failure (or) pump failure

Conditions producing type II respiratory failure

- Kyphoscoliosis
- Ankylosing spondylitis
- Obesity
- Myasthenia gravis
- Motor neuron disease
- Botulism
- Poisoning
- Acute severe asthma

(Kyphoscoliosis to Acute severe asthma: **Hypoventilation**)

- Foreign body obstructing air passage
- GBS

Gas exchange abnormalities

- Decrease $PaCO_2$
- Increase $PaCO_2$ ← CO_2 retention
- (A-a gradient) → normal

Hypoxia with hypercarbia

- Conditions may progress from Type-I to Type-II

Type 3 respiratory failure 00:19:18

- Post-surgical atelectasis

Type 4 respiratory failure 00:20:22

- Hypoperfusion of respiratory muscles
  - Shock – Cardiogenic shock
  - Hypovolemic shock.

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INTERSTITIAL LUNG DISEASE

Introduction 00:00:20

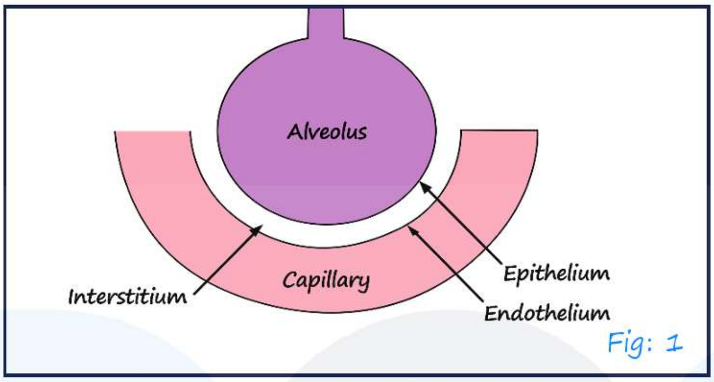
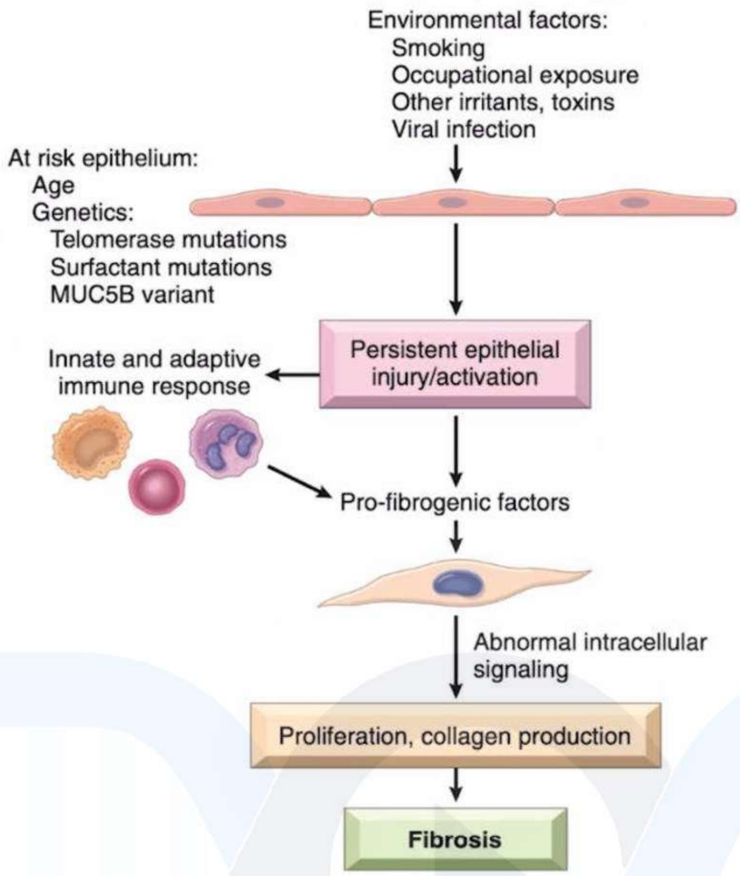


Fig: 1

- Involves
  - Lung interstitium (predominant)
  - Alveolar epithelium
  - Capillary endothelium
- Diffuse parenchymal lung disease
- Pathology: Lung inflammation and fibrosis of varying severity

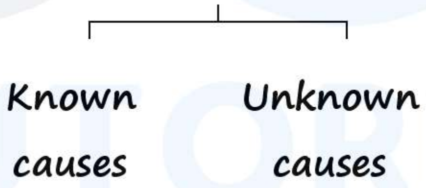
ILD

Known causes	Unknown causes



Classification 00:08:28

Classification of ILD



Known causes

- Exposure
  - Occupational exposure → Asbestosis, silicosis
  - Treatment
    i. Radiation
    ii. Methotrexate, amiodarone, nitrofurantoin, bleomycin, rituximab
- Associated with systemic diseases

Connective tissue diseases

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↓

Rheumatoid arthritis

Systemic sclerosis

Polymyositis/dermatomyositis

Vasculitis

↓

Granulomatosis poly angiitis

(Wegener's granulomatosis)

EGPA (churg straws syndrome)

- Granulomatous diseases → Hypersensitivity pneumonitis

Unknown causes

Idiopathic interstitial pneumonitis	**Others**
↓ Idiopathic pulmonary fibrosis Others	

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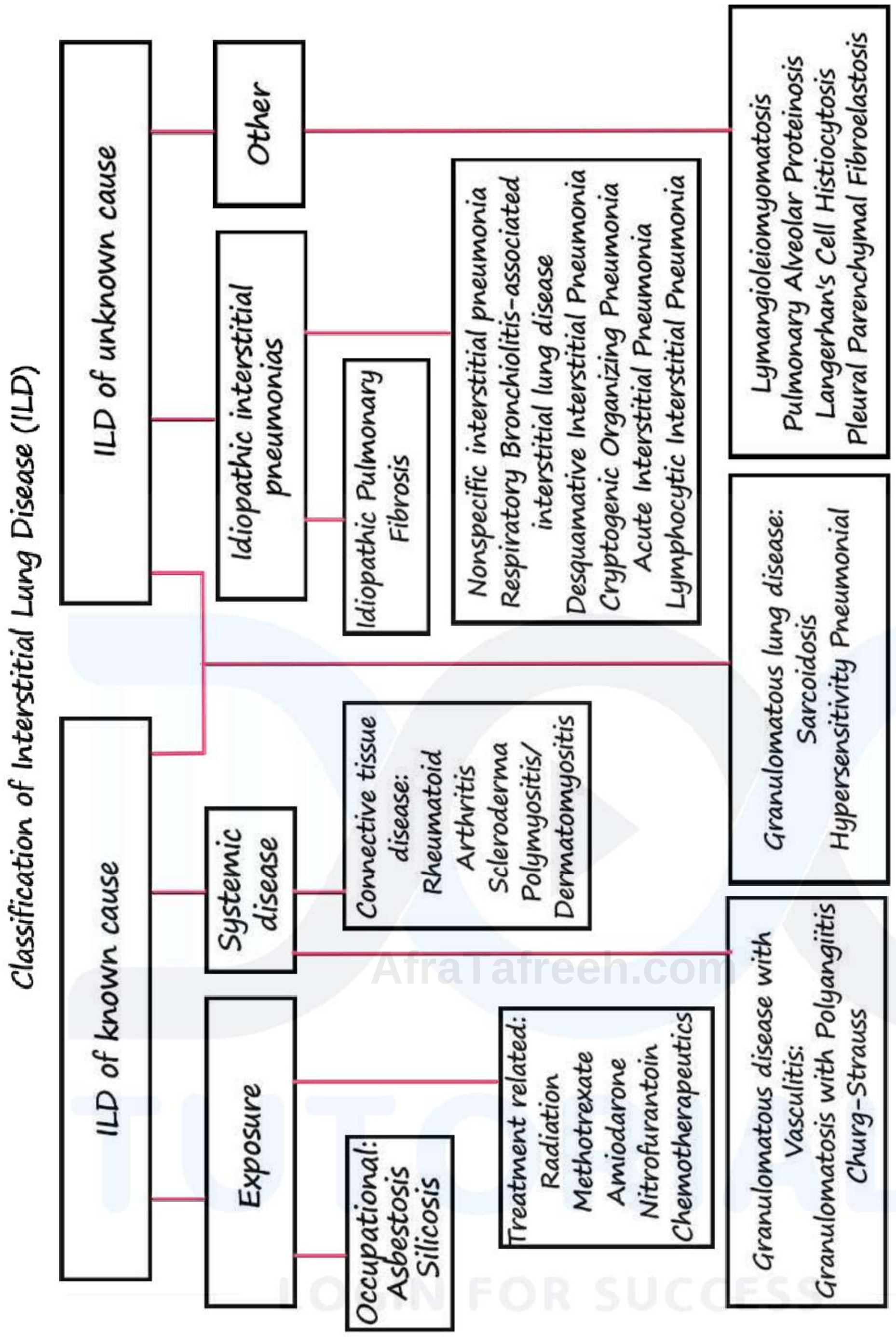

Idiopathic pulmonary fibrosis 00:16:12

- Chronic clinical presentation
- Males > Females, associated with smoking
- 5th and 6th decade
- Clinical features: Cough and dyspnoea on exertion
- O/E:
  - Clubbing

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- Crepitations, fine crackles which are late
- Inspiratory (Bibasal) fine crackles → Velcro crepitations

Investigations

i. CXR

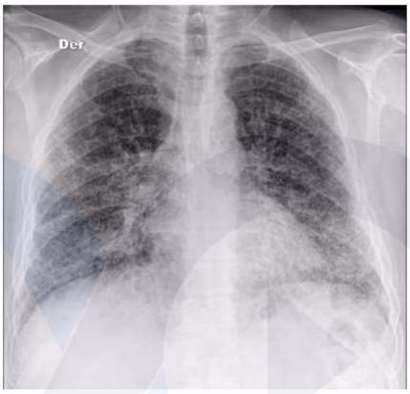

Fig: 2

Bibasal reticular infiltrates

ii. HRCT – IOC

- Pathology which happens → Usual Interstitial Pneumonia (UIP)
- HRCT
  - Posterior basal involvement
  - Subpleural involvement
  - Honey combing
  - Septal thickening
  - Traction bronchiectasis

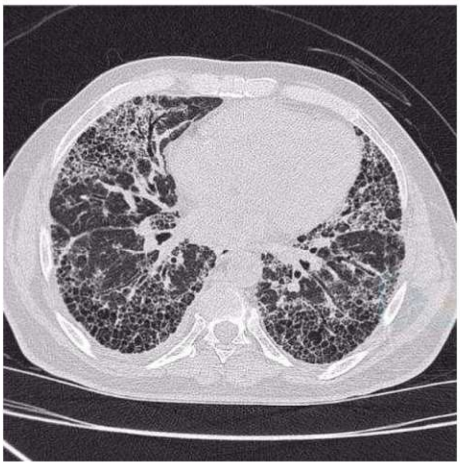

Fig: 3

iii. PFT – decrease TLC

$\frac{FEV1}{FVC}$ = Normal/increase

Decrease DLCO

Treatment

- 5-year mortality – 50%
- Nintedanib → Tyrosine kinase inhibitor

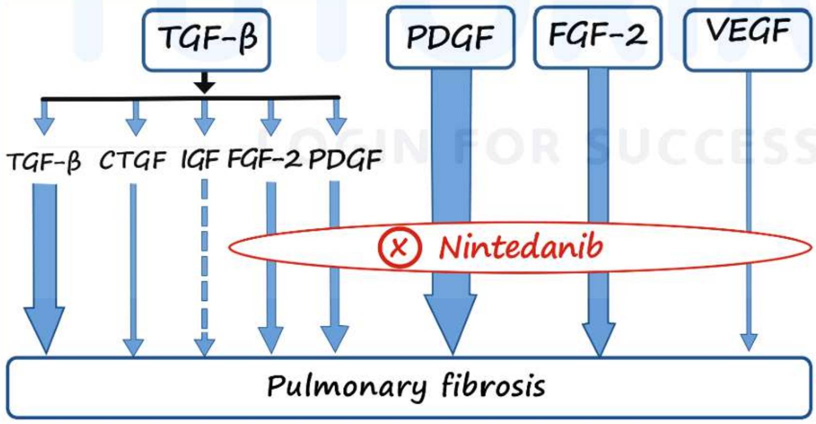

Fig: 4

- Lung transplantation

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NSIP – Non-Specific Interstitial Pneumonia

00:30:32

- 5th decade
- Females > Males
- Clinical features
  - Cough
  - Dyspnea on exertion
- Subacute disease course
- HRCT
  - Lung architecture relatively preserved
  - Ground glass opacities

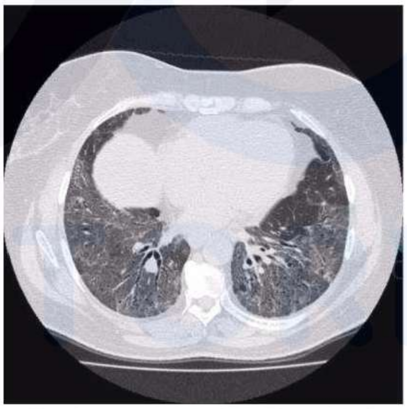

Fig: 5

- Treatment
  - Steroids
  - Rituximab
- NSIP
  i. Cellular
  ii. Fibrosing → poor prognosis
    - Certain cases can have mixed pattern (UIP+NSIP)

Smoking associated ILD 00:38:10

- Desquamative Interstitial Pneumonia (DIP)
- Respiratory bronchiolitis associated ILD

Cryptogenic Organizing Pneumonia (COP)

00:39:28

- Previously, Bronchiolitis Obliterans Organizing Pneumonia (BOOP)
- Treatment responsive to steroids

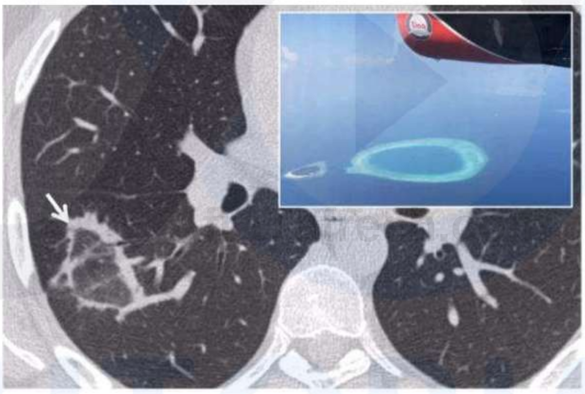

Fig: 6

Reverse halo sign/Atoll sign

↓

Central – ground opacity

Peripheral – consolidation

- Atoll-coral reef

Acute Interstitial Pneumonia (AIP) 00:42:38

- Mimics ARDS
- Hamman rich syndrome

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Lymphocytic Interstitial Pneumonia (LIP)00:44:04

- Seen in Sjogren's syndrome
  - Retroviral diseases

Lymphangioleiomyomatosis (LAM) 00:45:40

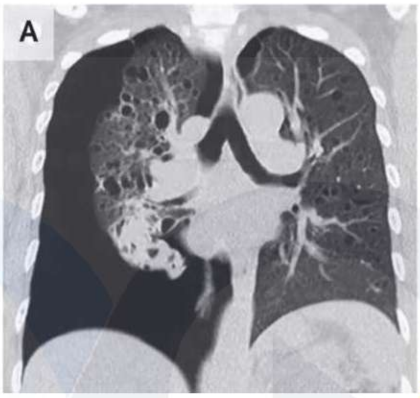

Fig: 7

- Seen in females (20-40years)
- Present with recurrent spontaneous pneumothorax
- Cystic changes ⊕

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Common Interstitial Lang Disease Findings

	IPF	Nonspecific Interstitial Pneumonia
Clinical symptoms	Gradual onset of SOB. dry cough. Unusual in younger adults.	Subacute onset of SOB, dry cough. Frequently associated with other conditions.
Physical examination findings	Frequent rales at lung bases, digital clubbing is common.	Frequent rales, Clubbing is less common.
Exposures	Idiopathic but many exposed to smoke. Genetic findings may explain >1/3 of the risk of the disease.	Can be idiopathic but should prompt consideration for associated conditions.
HRCT findings	Bilateral subpleural reticular changes most prominent in lower posterior lung zones. Traction bronchiectasis and honeycombing common Classic UIP pattern is considered diagnostic	Peripheral subpleural ground glass and reticular patterns. Traction bronchiectasis is common but honeycombing is rare. HRCT not diagnostic.
Histopathology	UIP pattern including fibroblastic foci, temporal and spatial heterogeneity, honeycombing	Cellular or fibrotic pattern of NSIP More uniform than a UIP pattern.
Clinical course	50% 3–5-year mortality	18% 5-year mortality

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Respiratory Bronchiolitis Associated ILD	Systemic Sclerosis Associated ILD	Sarcoidosis
Can be asymptomatic, or have SOB, and cough.	Gradual onset of SOB. dry cough. Fatigue. tightening of skin, exaggerated cold response, reflux, and difficulty swallowing	Can be asymptomatic, or have SOB, and cough. Can also have fatigue, palpitations, eye, skin, and joint findings
Rales common. Clubbing is rare	Can have rales in isolation. Also, skin thickening, joint swelling. and telangiectasias	Can be normal, rales may be present. Can have skin findings, joint pain, and enlarged lymph nodes
Strong association with smoking	Mostly unknown, some debate about solvent and silicate exposures	Mostly unknown, although silicate dusts thought to play a role in some cases
Diffuse patchy centrilobular ground glass nodules.	Can have UIP or INSIP patterns, also dilated esophagus, occasional mediastinal calcifications, and pulmonary vascular enlargement.	Can have mediastinal and hilar lymphadenopathy. Peribronchovascular reticular-nodular findings
Respiratory bronchiolitis with adjacent inflammatory and yand fibrosing changes. Pigment laden macrophages.	Both UIP or NSIP patterns can occur	Non-caseating granulomas
25% 7-year mortality	20-30% 10-year mortality	Generally low but varies by state

- In CTD
  - Systemic sclerosis
  - Polymyositis/dermatomyositis
  - Rheumatoid arthritis → UIP
- COP → may be associated with polymyositis.

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HYPERSENSITIVITY PNEUMONITIS

Introduction 00:00:20

- Hypersensitivity reaction to inhaled antigens
- Predominantly involves alveoli and small airways
- Type IV HS reaction → participation of TH_1 cells & TH_1 cells
- There is a role for innate immunity as well
- Varied antigens trigger
  - Bacterial
  - Fungal
  - Bird sources
  - Chemical exposure

Disease	Antigen	Source
Farming/Food Processing		
Farmer's lung	Thermophilic actinomycetes (e.g., Saccharopolyspora rectivirgula); fungus	Grain, moldy hay, silage
Bagassosis	Thermophilic actinomycetes	Sugarcane
Cheese washer's lung	Penicillium casei; Aspergillus clavatus	Cheese
Coffee worker's lung	Coffee bean dust	Coffee beans
Malt worker's lung	Aspergillus species	Barley
Miller's lung	Sitophilus granarius (wheat weevil)	Wheat flour
Mushroom worker's lung	Thermophilic actinomycetes: mushroom spores	Mushrooms
Potato riddler's lung	Thermophilic actinomycetes: Aspergillus species	Moldy hay around potatoes
Tobacco grower's lung	Aspergillus species	Tobacco
Wine maker's lung	Botrytis cinerea	Grapes

Birds and Other Animals		
Bird fancier's lung (also named by specific bird exposures)	Proteins derived by parakeets, pigeons, budgerigars	Bird feathers, droppings, serum proteins
Duck fever	Duck feathers, serum proteins	Ducks
Fish meal worker's lung	Fish meal dust	Fish meal
Furrier's lung	Dust from animal furs	Animal furs
Laboratory worker's lung	Rat urine, serum, fur	Laboratory rats
Pituitary snuff taker's lung	Animal proteins	Pituitary snuff from bovine and porcine sources
Poultry worker's lung	Chicken serum proteins	Chickens
Turkey handling disease	Turkey serum proteins	Turkeys
	Proteins derived by parakeets, pigeons, budgerigars	Bird feathers, droppings, serum proteins

Other Occupational and Environmental Exposures		
Chemical worker's lung	Isocyanates	Polyurethane foam, varnish, lacquer
Detergent worker's lung	Bacillus subtilis enzymes	Detergent
Hot tub lung	Cladosporium species; Mycobacterium avium complex	Contaminated water, mold on ceiling
Humidifier fever (and air conditioner lung)	Several microorganisms including: Aureobasidium pullulans; Candida albicans; thermophilic actinomycetes; Mycobacterium species; Klebsiella oxytoca; Naegleria gruberi	Humidifiers and air conditioners (contaminated water)
Machine operator's lung	Pseudomonas species; Mycobacteria species	Metal working fluid
Sauna taker's lung	Aureobasidium species; other antigens	Sauna water
Suberosis	Penicillium glabrum; Chrysonilia sitophila	Cork dust
Summer-type pneumonitis	Trichosporon cutaneum	House dust mites, bird droppings

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Clinical features 00:12:30

- Acute: - 4-8hrs of exposure
- Subacute
- Chronic

(Acute, Subacute, Chronic) — Respiratory symptoms, Systemic symptoms ↓ **Fever, fatigue**

- Acute: self-resolving
- Subacute:
  - Days of weeks
  - Self-resolving
- Chronic:
  - Slowly progressive, months
  - Weight loss
  - Clubbing
  - Fibrosis sets in

Investigation 00:18:20

- CXR: nonspecific finding
- HRCT: Ground glass opacities → Mosaic pattern
  - Centrilobular nodules

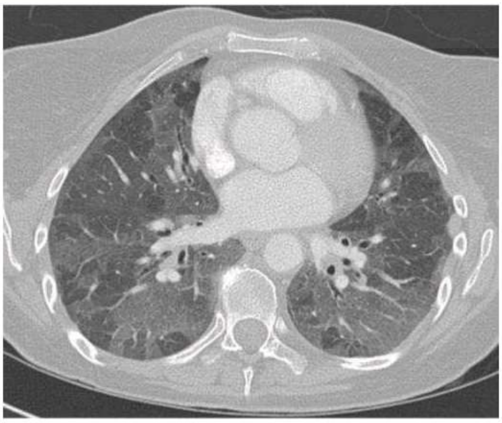

Fig: 1

- Pulmonary function tests

- Restrictive
- Obstructive

- Farmer's lung – emphysematous
- DLCO decreased
- Serum precipitins – IgG Ab against specific antigens
- Bronchoscopy & BAL study
- Bronchoalveolar lavage fluid:
  - Increase BAL lymphocytes
  - CD_4/CD_8 ratio < 1
- Transbronchial biopsy
  - Non caseating granulomas
  - NSIP
  - UIP

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Differential diagnosis 00:26:30

- ILD
- Sarcoidosis

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Treatment 00:27:00

- Acute: – Self resolving
- Subacute & chronic → steroids
  - To avoid further exposure of antigen.

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PLEURAL EFFUSION

Introduction 00:00:36

- In pleural space normally around 5ml – 20ml of fluid (+)
- Pleural fluid is formed from parietal pleura capillaries at the rate of 0.01ml/1kg 1hour
- Reabsorption of fluid formed is by lymphatics

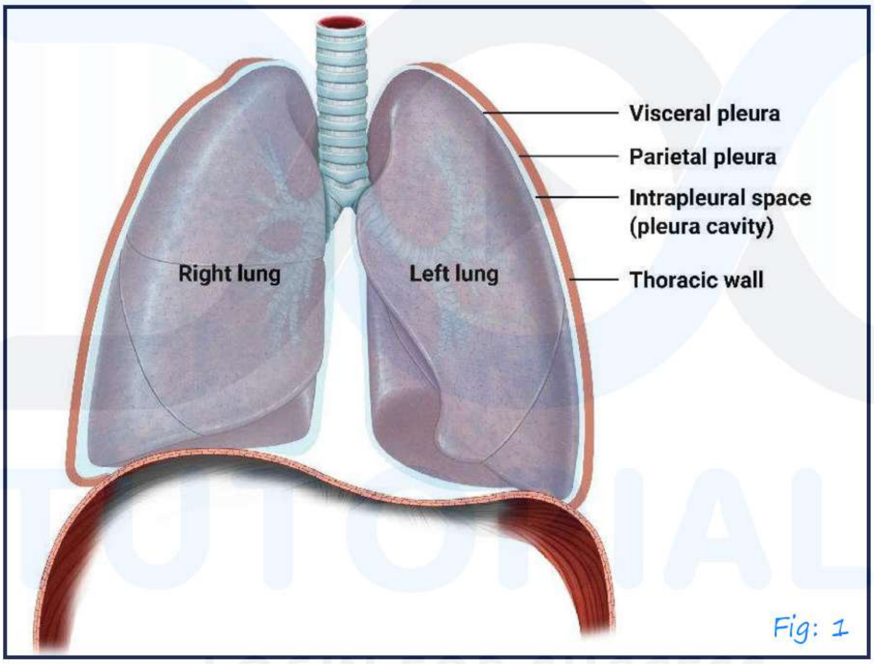

Fig: 1

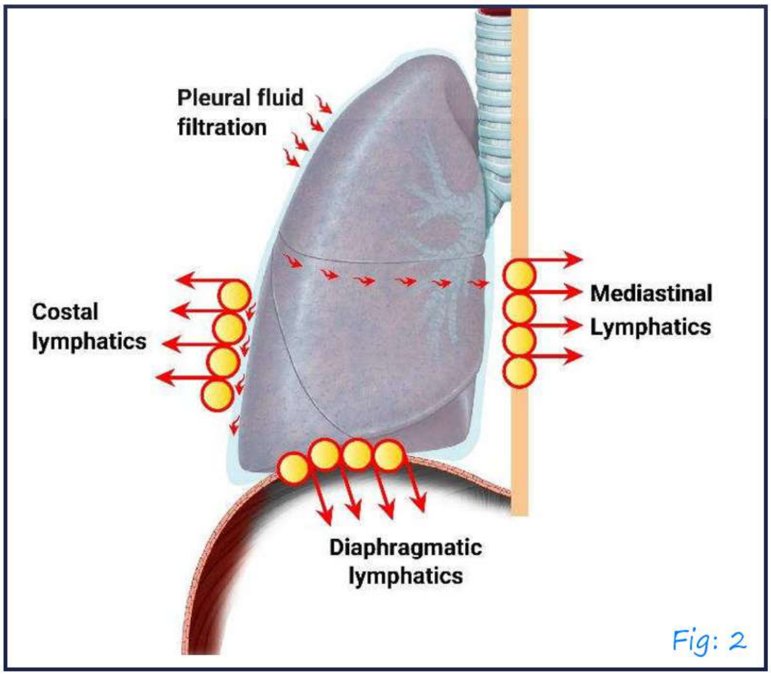

Fig: 2

- Fluid can either be
  - Transudate
  - Exudate
  - Pus
  - Blood
  - Chyle

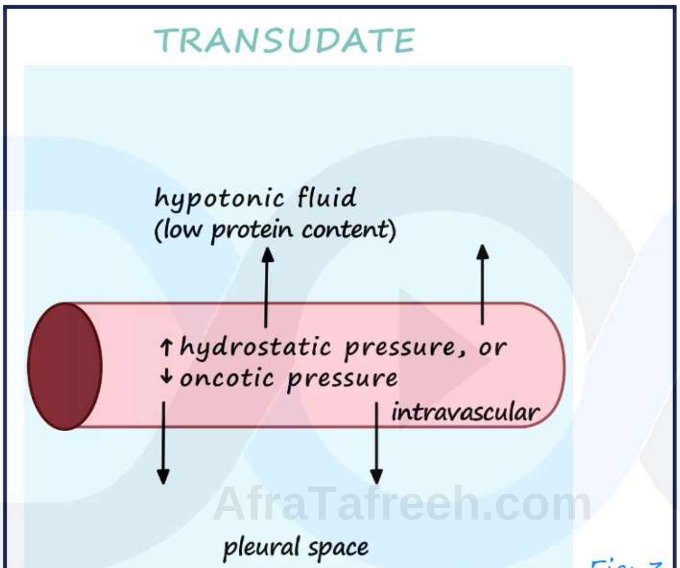

Fig: 3

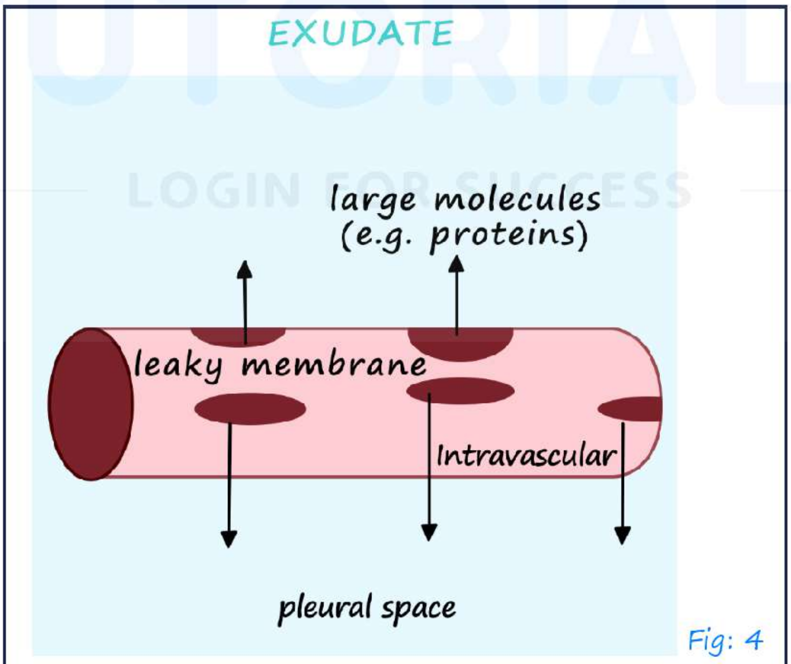

Fig: 4

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Transudative 00:04:52

- Due to imbalance between hydrostatic and oncotic pressure
- Oncotic pressure is predominantly contributed by plasma proteins
- Hydrostatic pressure – Oncotic pressure is high

  ↓

  Ultrafiltration of plasma

Exudative 00:08:48

- Due to disease involving pleura
- During filtration, some of the plasma proteins leak into pleural space
- Fluid is similar to plasma fluid.

Causes 00:11:28

Causes of Transudative pleural effusion → B/L effusion

- Most common cause - congestive cardiac failure → ↑ Hydrostatic pressure
- Cirrhosis
- Nephrotic syndrome
- Contractive pericarditis
- SVE obstruction
- Myxedema
- Peritoneal dialysis
- Urinothorax

Causes of Exudative Effusion – Either u/L or B/L effusion

- Most common cause – syn pneumonic para-pneumonic (mild → moderate)
- Malignancies
- TB
- Connective tissue diseases
  - Rheumatoid arthritis
  - Sjogren's syndrome
  - SLE
- Acute pancreatitis } (L)sided pleural effusion
- Esophageal rupture }
- Meigs syndrome (ovarian fibroma/ Thecoma)

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Exudative Pleural Effusions

1. Neoplastic diseases
   a. Metastatic disease
   b. Mesothelioma
2. Infectious diseases
   a. Bacterial infections
   b. Tuberculosis
   c. Fungal infections
   d. Viral infections
   e. Parasitic infections
3. Pulmonary embolization
4. Gastrointestinal disease
   a. Esophageal perforation

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b. Pancreatic disease

c. Intraabdominal abscesses

d. Diaphragmatic hernia

e. After abdominal surgery

f. Endoscopic variceal sclerotherapy

g. After liver transplant

5. Collagen vascular diseases

a. Rheumatoid pleuritis

b. Systemic lupus erythematosus

c. Drug-induced lupus

d. Sjögren syndrome

e. Granulomatosis with polyangiitis (Wegener)

f. Churg-Strauss syndrome

6. Post-coronary artery bypass surgery

7. Asbestos exposure

8. Sarcoidosis

9. Uremia

10. Meigs' syndrome

11. Yellow nail syndrome

12. Drug-induced pleural disease

a. Nitrofurantoin

b. Dantrolene

c. Methysergide

d. Bromocriptine

e. Procarbazine

f. Amiodarone

g. Dasatinib

13. Trapped lung
14. Radiation therapy
15. Post-Cardiac injury syndrome
16. Hemothorax
17. Iatrogenic injury
18. Ovarian hyperstimulation syndrome
19. Pericardial disease
20. Chylothorax

Light's criteria: - (Any 1 (+) → exudative effusion)

00:23:48

1. $\frac{\text{Pleural fluid protein}}{\text{S. protein}} > 0.5$
2. $\frac{\text{Pleural fluid LDH}}{\text{S. LDH}} > 0.6$
3. Pleural fluid LDH > 2/3 of upper level in serum
   - 25% of transudates may be misdiagnosed as exudates based on this criterion

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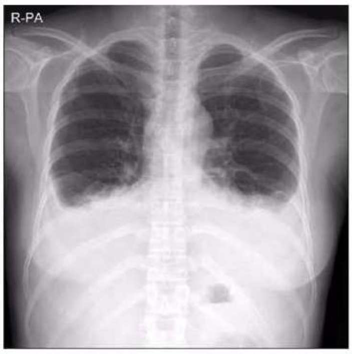

Fig: 5

- x-ray PA view → 200 ml of fluid
- Clinical examination → 300 ml of fluid
- Most sensitive to detect a effusion - CT thorax

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- USG thorax - minor effusion
- X-ray lateral decubitus - 50 ml of fluid

Fig: 6

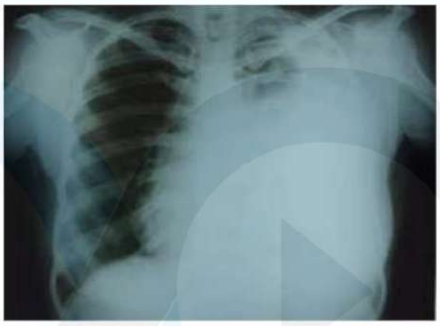

Fig: 7

- In massive effusion, lying on opposite side causes breathlessness Treponema

Fig: 8

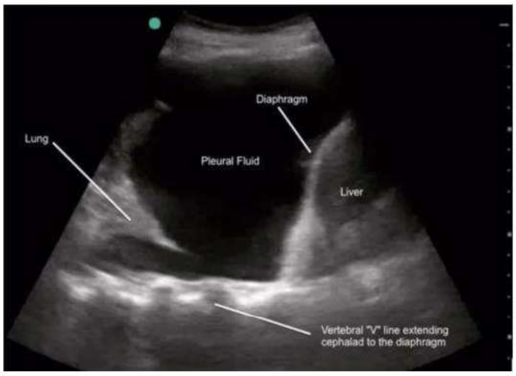

Fig: 9

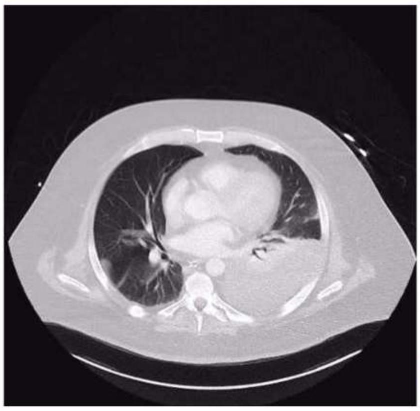

Fig: 10

Fig: 11

Definite air fluid level

↓

(R) Hydropneumothorax

- Presence of pus in pleural cavity → Empyema
- Complicated parapneumonic effusion → Empyema & Loculi
- Blood in pleural cavity – Hemothorax

↓

$\frac{\text{Pleural fluid hematocrit}}{\text{Plasma fluid HCT}} > 0.5$

- Seen in trauma
- Malignancy
- Mesothelioma
- TB

- Chyle in pleural cavity – Chylothorax → Trauma

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Chyliform effusion	Pseudostyles effusion
• Due to ↑ Chylomicrons & ↑ Triglycerides	• Due to rheumatoid arthritis (Cholesterol Crystals)

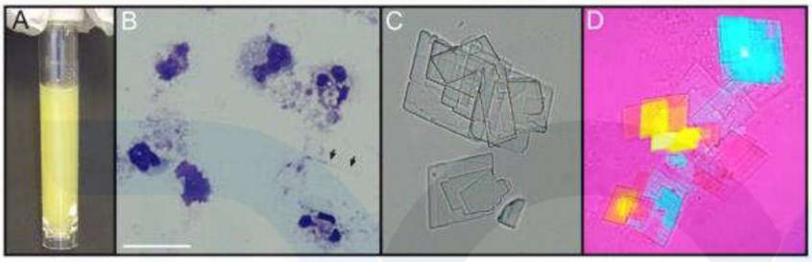


Fig: 12

- Wright stain
- Wet mount preparation → Shattered glass appearance

Diagnostic Algorithm of Pleural Effusion

Pleural effusion

↓

Perform diagnostic thoracentesis

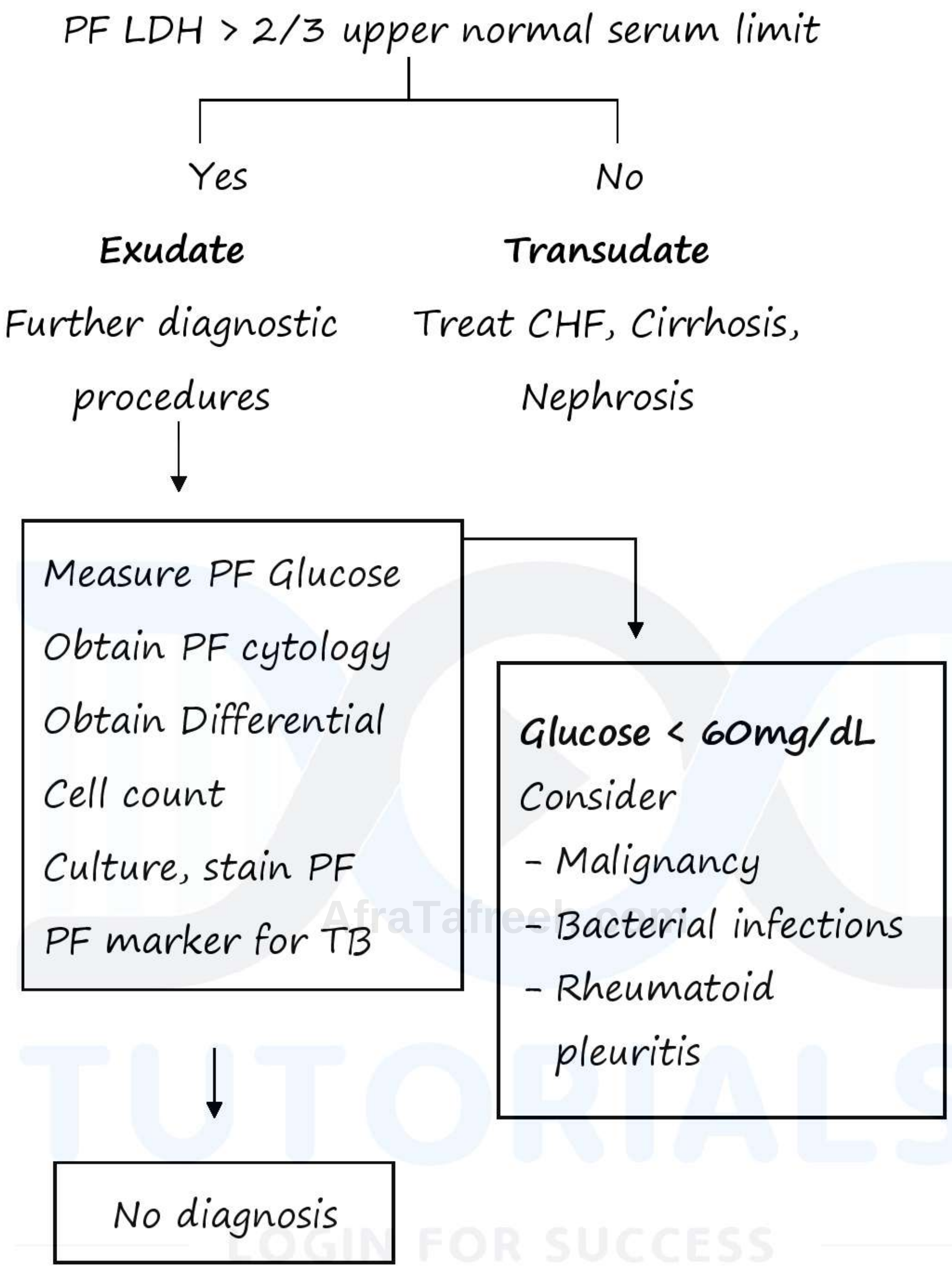
Measure pleural fluid protein and LDH

↓

Any of following met?

PF/serum protein >0.5

PF/Serum LDH > 0.6



- Vocal Fremitus
- Vocal Resonance
- Stony dullness
- Increased or absent breath sounds

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Thoracocentesis: 00:46:04

- Ideal space is 7th ICS in midscapular line

Fig: 13

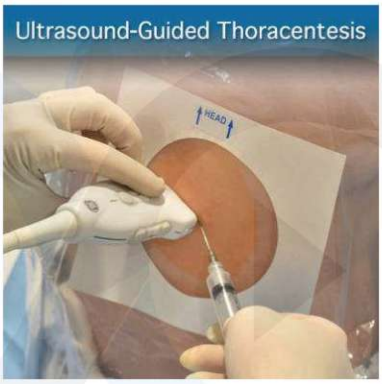

Fig: 14

- Malignant cytology
- Thoracoscopy and biopsy
- Pleural fluid
  - Gram Stain
  - Culture
  - CB WAAT (43%)
- Pleural biopsy CB NAAT
- Pulmonary embolism producing pleural effusion may be transudate or exudate
- Urinothorax: ↑ creatinine levels

Fig: 15

ICD Indication 00:57:36

- Pleural fluid pH <7.2
- Loculated effusion
- Empyema
- Positive gram stain
- Positive culture
- ICD insertion in midaxillary line 5th ICS
- Do not remove > 1.5 liters at a time

  ↓

  Chance of re-expansion pulmonary edema
- Malignant pleural effusion requiring frequent tapping

  ↓

  Injury doxycycline in pleural cavity

  ↓

  Adhesions (Pleurodesis).

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PNEUMOTHORAX

- Excess air in pleural cavity
- Intrapleural pressure in normal individuals is negative.

Classification 00:02:10

i. Non-traumatic (spontaneous)

ii. Traumatic

Non-traumatic (spontaneous)

- **Primary** → No underlying lung d/s → Tall, Thin, Smokers
- **Secondary** → Under lying lung d/s → COPD

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Traumatic

- **Iatrogenic** → Central vein catheterization, Bronchial biopsy
- **Non-Iatrogenic** → Penetrating injury, Blunt trauma

Causes of non-traumatic spontaneous pneumothorax

Primary Pneumothorax	Secondary Pneumothorax
Asthenic body habitus/subpleural blebs	**Airway disease**
Drug Use - Cigarette smoking - Snorting cocaine - Smoking marijuana	**Airway disease** - Cystic fibrosis - Asthma - COPD
Increased transpulmonary pressure - Valsalva maneuver - Diving, military flying	**Infection** - Pneumocystis jiroveci (carinii) - Tuberculosis - Necrotizing pneumonia
	Congenital lung disease - Congenital pulmonary adenomatous malformation - Congenital lobar emphysema
	Interstitial lung disease - Sarcoidosis - Langerhans cell granulomatosis - Other
	Connective tissue/inflammatory disease - Marfan syndrome - Elhers – Danlos syndrome - Juvenile idiopathic arthritis polymyositis or dermatomyositis - Birt-Hogg-Dube syndrome - Other
	Malignancy - Primary lung cancer - Metastatic disease
	Airway Obstruction - Foreign body aspiration
	Thoracic endometriosis - Catamenial pneumothorax

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Pneumothorax

- Closed
- Open
- Tension

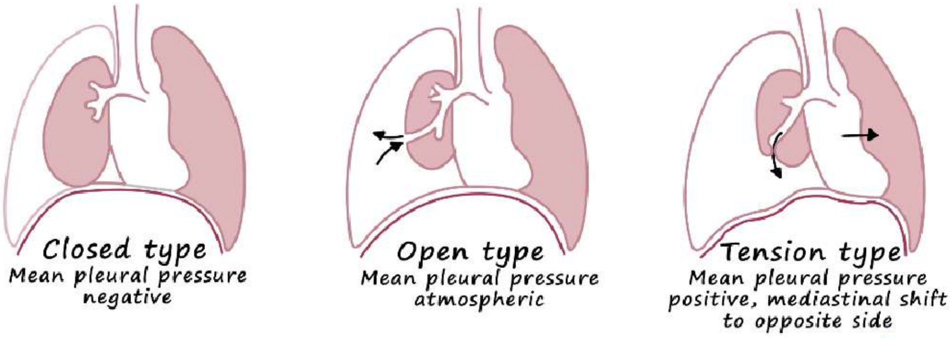

Fig: 1

Clinical features 00:14:57

- Acute onset of breathlessness

  Decrease venous return

  ↓

  Decrease Co

  ↓

  Shock/hemodynamic compromise

- Cyandsis

O/E

- Tachyphea
- Tachycardia
- Cynaosis
- Decrease systolic BP
- Decrease chest expansion
- Decrease VF, decrease VR
- Hyper-resonant node
- Absent breath sounds

- Pneumomediastinum → Hamman's mediastinal crunch

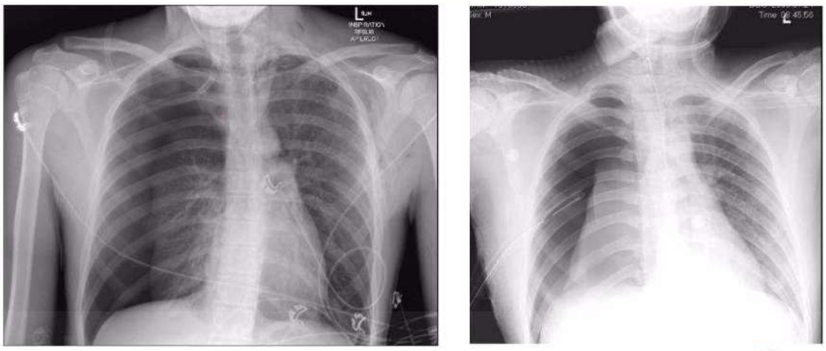

Fig: 2

Right sided pneumothorax
↓
Deep sulcus sign (supine x-ray)

Treatment 00:23:41

- British thoracic society guidelines (BTS guidelines)
- Tension pneumothorax → Insert large bore needle in 2nd ICS in the midclavicular line
↓
Hissing sound

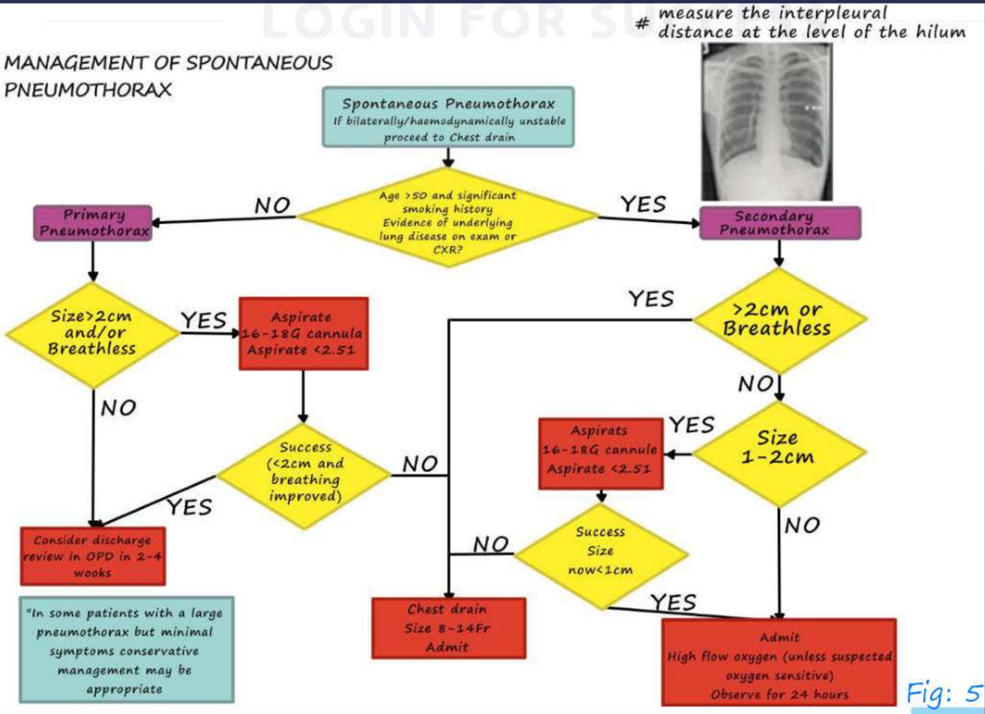

Fig: 5

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- Chest tube usually inserted in 5th ICS – midaxillary line

↓

Connected to underwater seal

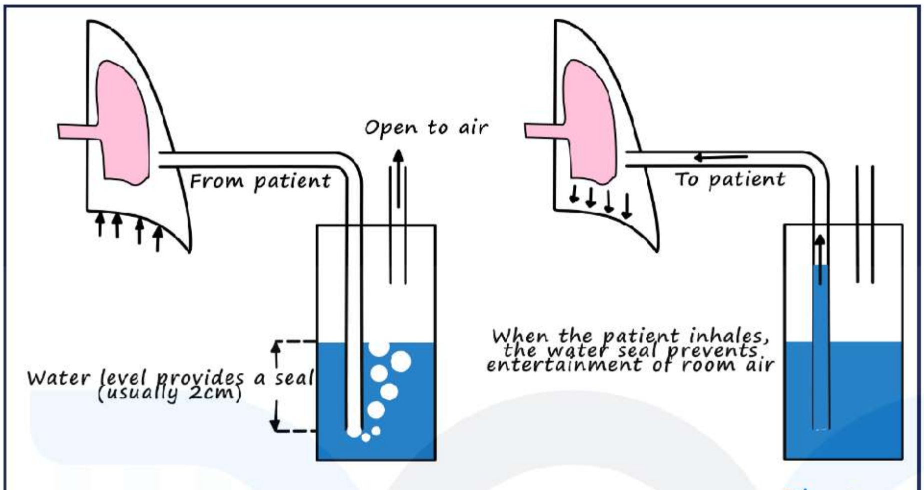

Fig: 6

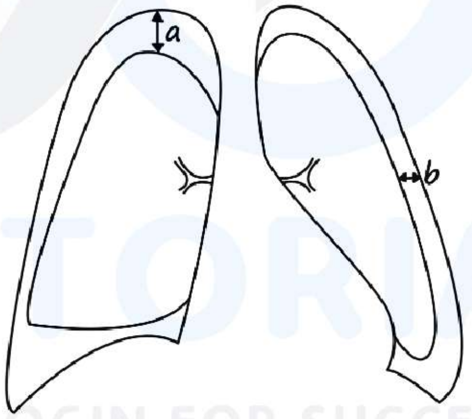

Fig: 7

a=apex to cupola distance-American Guidelines

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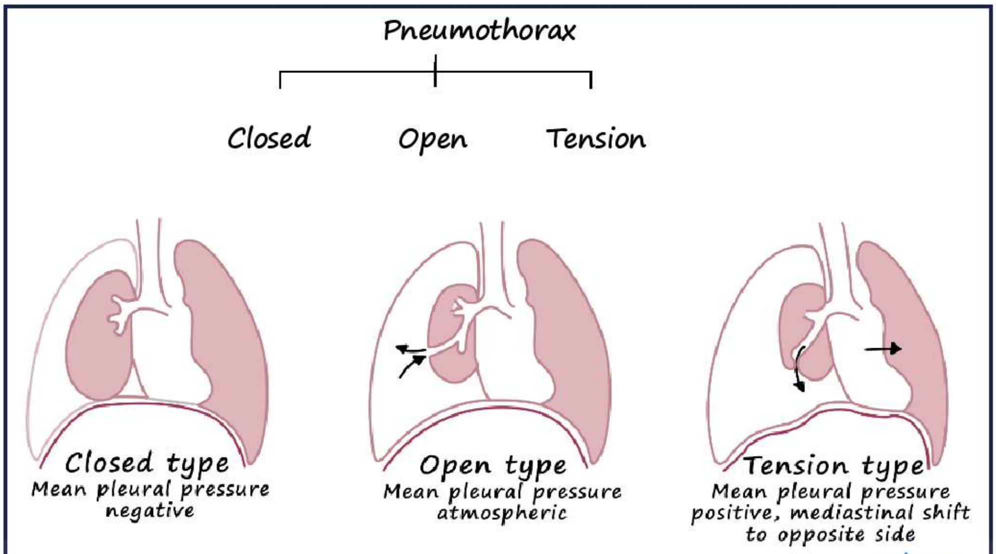

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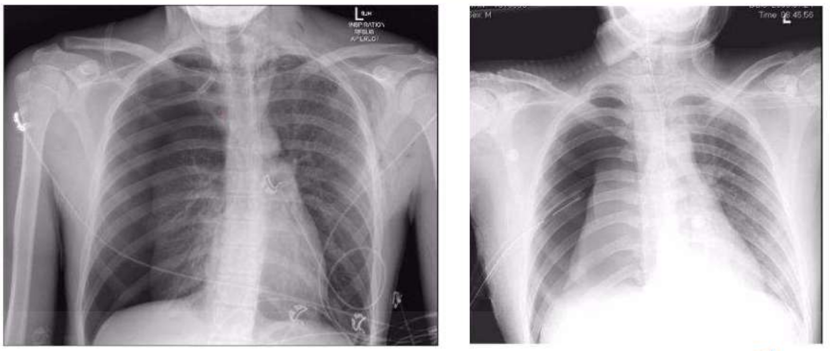

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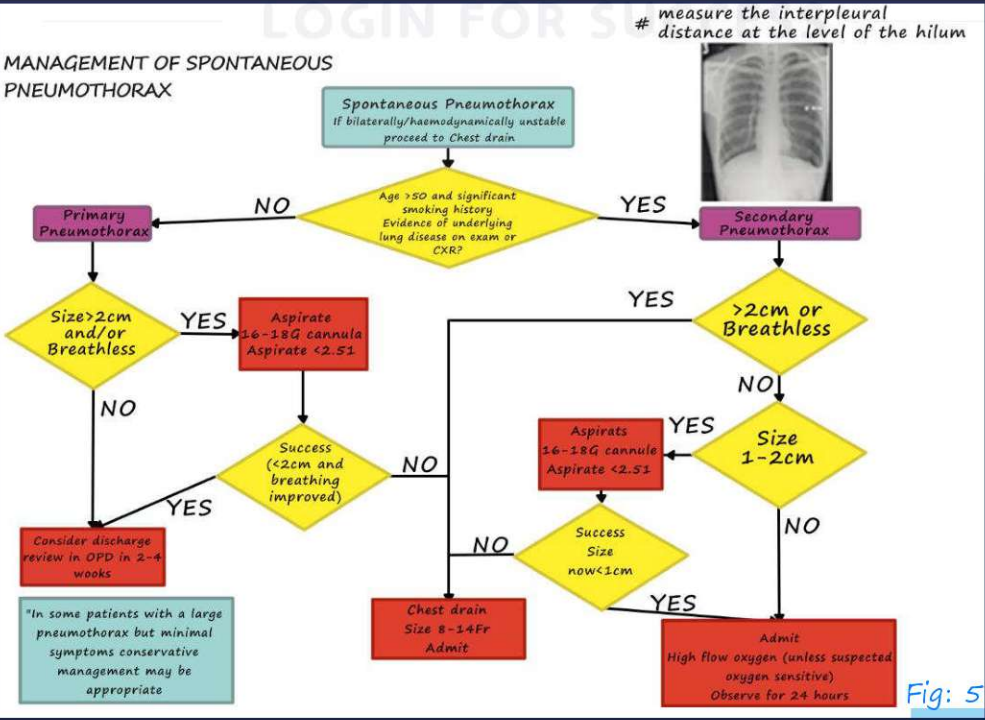

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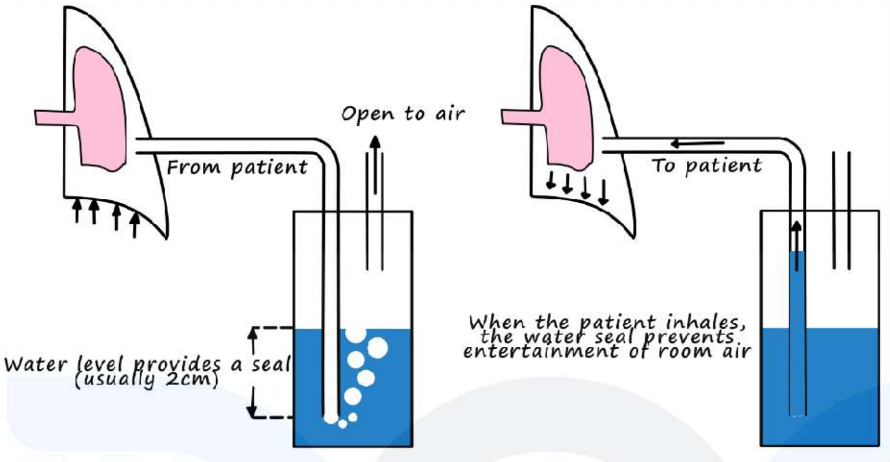

Fig: 6

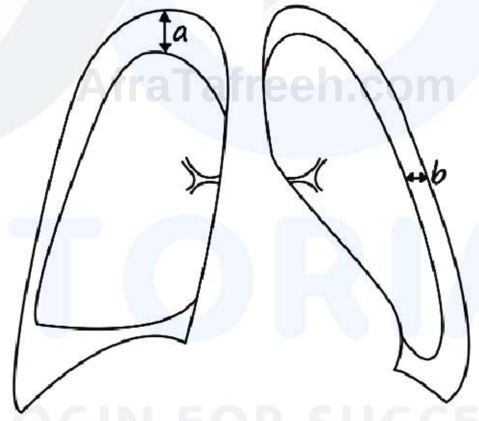

Fig: 7

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PNEUMOCONIOSIS

Introduction 00:00:16

- Occupational lung diseases
  - Refers to a group of chronic fibrosing diseases
  - Occurs due to exposure to inorganic/organic dust
  - Depends on size (1-5μm) solubility of dust particle

Asbestosis 00:03:34

- Asbestosis exposure
  - 90% serptine form → chrysotile form
  - Amphibole form (10%)
    - i. Crocidolite
    - ii. Amosite

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Clinical features

- Usually takes atleast 10years to manifest from the time of exposure
- Pleural plaques (most common)
- Pleural effusion
- Diffuse interstitial fibrosis
- Ca lung
- Mesothelioma
  - Pleural plaques → fibrosis of pleura + calcification
  - Pleural effusion → exudative effusion – contain eosinophils (serous/bloody)

- Diffuse interstitial fibrosis → Bilateral, involves lower zones
- Increased risk of malignancy in smokers
- Asbestos → absorb toxic chemicals from tobacco
- Mesothelioma can occur
  i. Pleural
  ii. Peritoneal

Clinical features

- Dyspnea on exertion (most common)
- Cough
- Hemoptysis
- Weight loss

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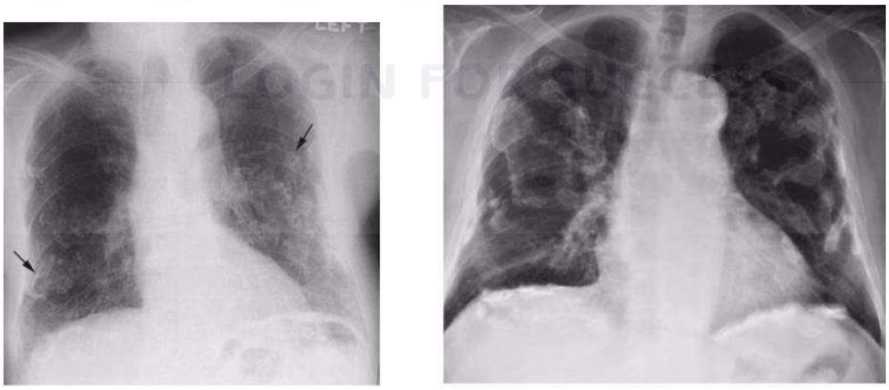
PFT

- Restrictive pattern



Bilateral pleural plaques Fig: 1

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Holy leaf sign Fig: 2

HRCT

- Ground glass opacities
- Reticular pattern
- Honey combing

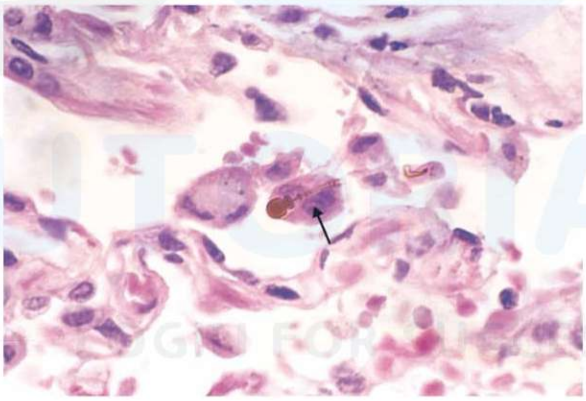

Fig: 3

  - Asbestos bodies
  - Ferruginous bodies
- Asbestosis associated with
  - Mining industry
  - Milling
  - Textile
  - Cement manufacturing

Silicosis 00:18:18

- Exposure to free silica – silicon dioxide

Silicon dioxide

- Amorphous form
- Crystalline form

Silicosis

- Acute → 10 months
- Chronic → 15 years

Acute silicosis

- Similar to primary alveolar proteinosis

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Fig: 4

Ground glassing ⊕

Thickened interlobular &

Intralobular septa

↓

Crazy pavement pattern

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Chronic silicosis

- Working in stone cutting industry
  - Sand blasting industry
  - Miners
- Can present as
  - i. Simple silicosis
    - Nodules <1cm lung function
  - ii. Complicated silicosis
    - Nodules >1cm impaired lung function may progress to
    - Progressive Massive Fibrosis (PMF)

Fig: 5

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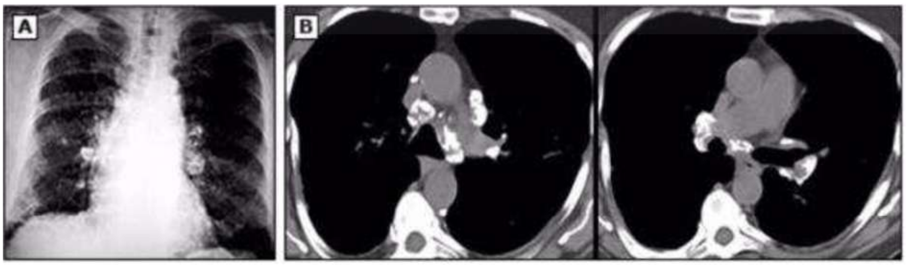

Egg shell calcification

Fig: 6

Silicotuberculosis

- Silica interferes with pulmonary alveolar macrophages
- Fibrosis is towards upper zone

Coal workers pneumoconiosis 00:29:36

- Coal miners
- Can present → simple coal workers pneumoconiosis (nodules <1cm)

↓

Complicated workers pneumoconiosis (nodules >1cm)

↓

Progresses to massive fibrosis

- Refers to black lung

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Fig: 7

Complicated coal workers pneumoconiosis

↓

PMF

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Occupational Exposures	Nature of Respiratory responses	Comment
Inorganic Dusts		
Asbestos: mining, processing, construction, ship repair	Fibrosis (asbestosis), pleural disease, cancer, mesothelioma	Virtually all new mining and construction with asbestos done in developing countries
Silica: mining, stone cutting, sandblasting, quarrying	Fibrosis (silicosis), progressive massive fibrosis (PMF), cancer, tuberculosis, chronic obstructive pulmonary disease (COPD)	Improved protection in United States; persistent risk in developing countries
Coal dust: mining	Fibrosis (coal worker's pneumoconiosis), PMF, COPD	Risk persists in certain areas of United States, increasing in countries where new mines open
Beryllium: processing alloys	Acute pneumonitis (rare), chronic	Risk in high-tech industries persists

for high-tech industries	granulomatous disease, lung cancer (highly suspect)	
Other metals: aluminium, chromium, cobalt, nickel, titanium, tungsten carbide, or "hard metal" (contains cobalt)	Wide variety of conditions from acute pneumonitis to lung cancer and asthma	New disease appear with new process development
Organic dusts		
Cotton dust: milling, processing	Byssinosis (an asthma-like syndrome), chronic bronchitis, COPD	Increasing risk in developing countries with drop in United States as jobs shift overseas
Grain dust: elevator agents, dock workers, milling, bakers	Asthma, chronic bronchitis, COPD	Risk shifting more to migrant labor pool
Other agricultural dusts: fungal spores, vegetable products, insect fragments, animal dander, bird and rodent feces,	Hypersensitivity pneumonitis (farmer's lung), asthma, chronic bronchitis	Important in migrant labor pool but also resulting from in home exposures

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endotoxins, microorganisms, pollens		
Toxic chemicals: wide variety of industries	Asthma, chronic bronchitis, COPD, hypersensitivity pneumonitis, pneumoconiosis, and cancer	Reduced risk with recognized hazards; increasing risk of developing countries where controlled labor practices are less stringent
Other Environmental agents		
Uranium and radon daughters, secondhand tobacco smoke, polycyclic aromatic hydrocarbons (PAHs), biomass smoke, diesel exhaust, welding fumes, wood finishing	Occupational exposures estimated to contribute to up to 10% of all lung cancers; chronic bronchitis, COPD, and fibrosis	In-home exposures important; in developing countries, biomass smoke is a major risk factor for COPD among women in these countries.

- Byssinosis also refers to Monday chest tightness.

OBSTRUCTIVE SLEEP APNE

Introduction 00:00:29

- ICSD – III: international classification of sleep disorders
- The third edition of the International Classification of Sleep Disorders (ICSD-III: Diagnostic and Coding Manual, 2014; American Sleep Disorders Association, Rochester, MN) includes seven major categories of sleep disorders:

  1.Insomnia

  2.Sleep-related breathing disorders

  3.Central disorders of hypersomnolence

  4.Circadian rhythm sleep-wake disorders

  5.Parasomnias

  6.Sleep-related movement disorders

  7.Other sleep disorders

- Sleep related breathing disorders

  ↓

  OSAS

  CSA (Central sleep APNEA)

- Characterized by ventilation problem
  - Disruption of sleep
  - Excessive day time sleepiness/fatigue

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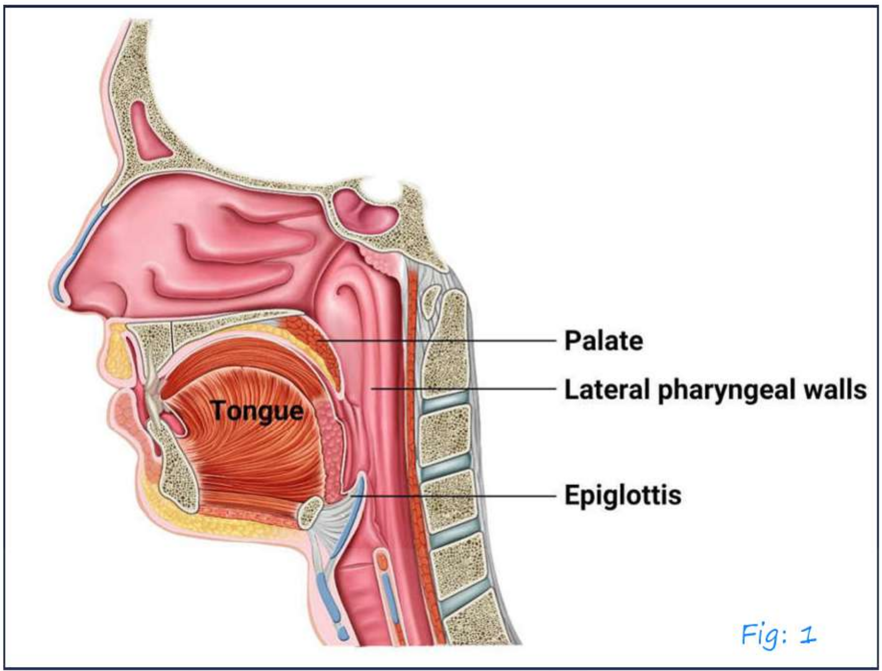

Fig: 1

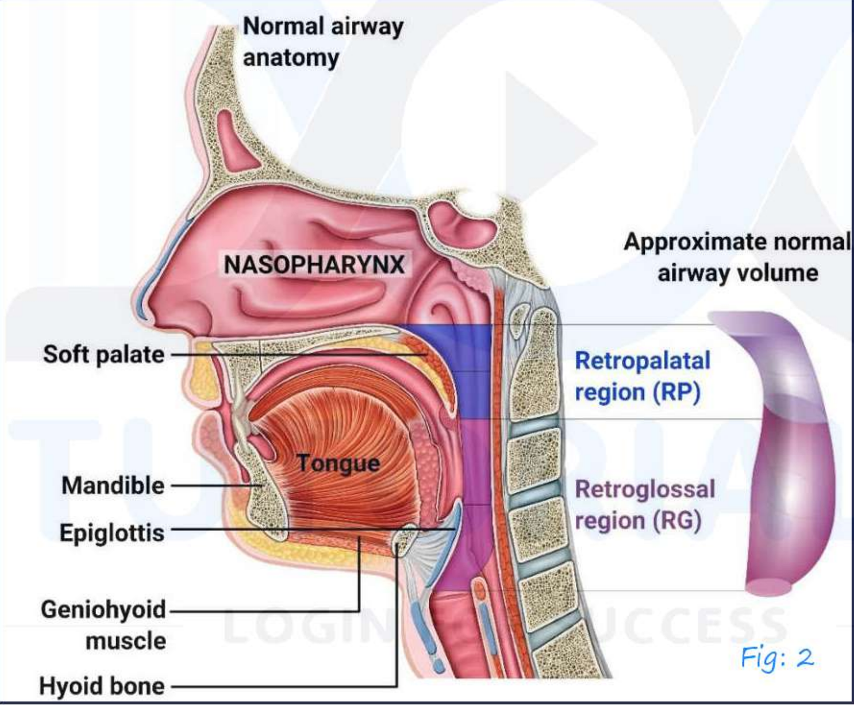

Fig: 2

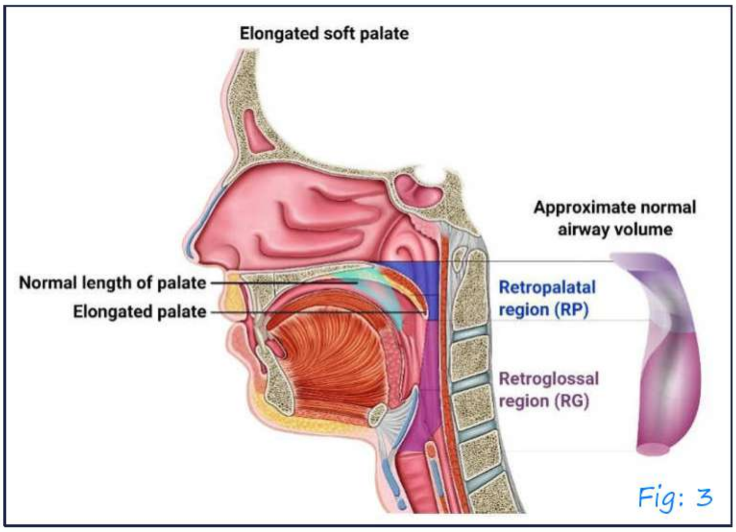

Fig: 3

- Elongated soft palate → Most common reason for OSA
- In REM stage of sleep there is decreased input to the neuromuscular junction & muscles

↓

↓ In tone of muscle

↓

Airway compromised

- Increased tongue fat and inferior hyoid position

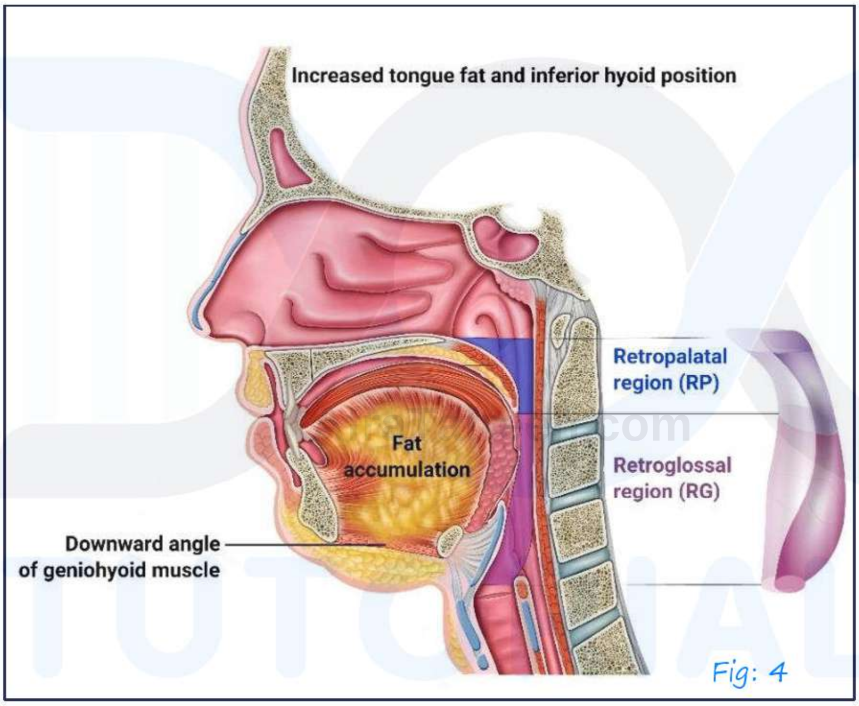

Fig: 4

- Increased fat in lateral pharyngeal wall

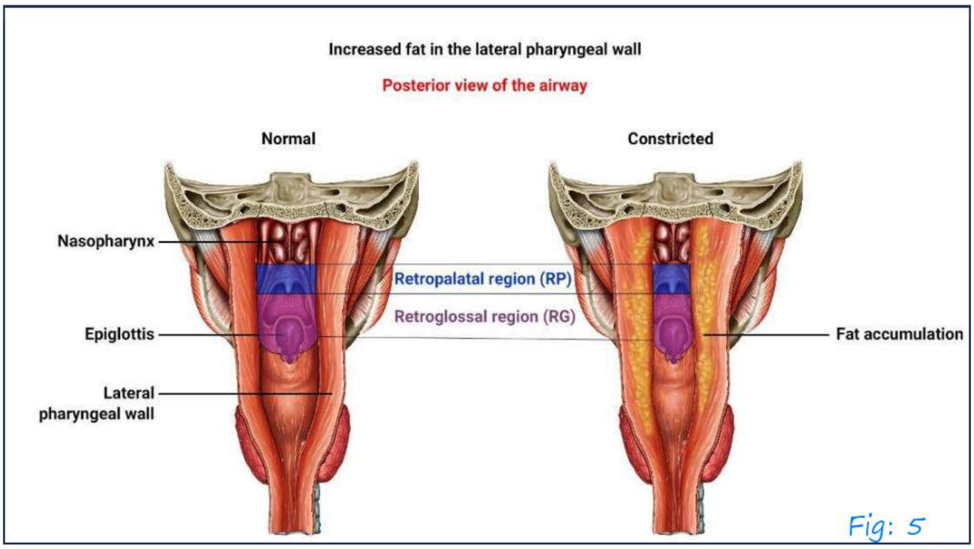

Fig: 5

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- Shortened mandible

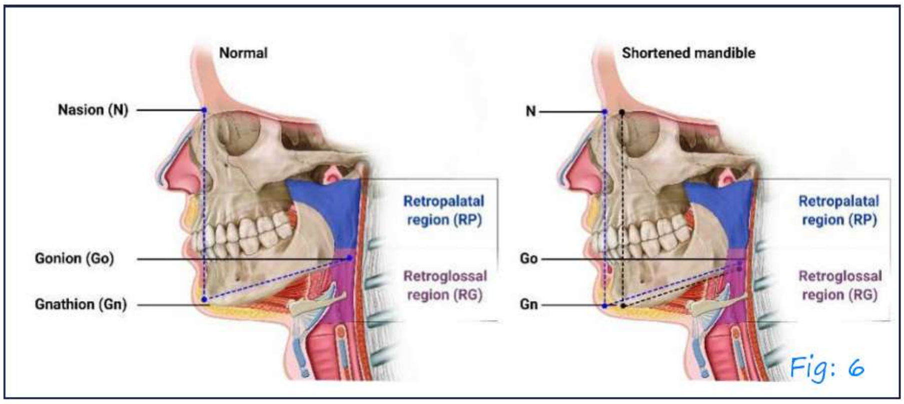

Fig: 6

- Skeletal abnormalities
  - Micrognathia
  - Retrognathia
  - Treacher collins syndrome
  - Down's syndrome
- Obesity

Clinical Features 00:15:38

- Night time symptoms
- Day time symptoms

DOC TUTORIALS LOGIN FOR SUCCESS

Night time symptoms

- Snoring
- Snorting
- Gasping
- Breathing pauses

Day time symptoms

- Excessively sleeps
- Fatigue

Nocturnal Symptoms During Sleep

- Loud snoring (often with a long history)
- Choking during sleep
- Cessation of breathing (apneas witnessed by bed partner)
- Sitting up or fighting for breath
- Abnormal motor activities (e.g., thrashing about in bed)
- Severe sleep disruption
- Gastroesophageal reflux causing heartburn
- Nocturia and nocturnal enuresis (mostly in children)
- Insomnia (in some patients)
- Excessive nocturnal sweating (in some patients)

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Daytime Symptoms

- Excessive daytime somnolence
- Forgetfulness
- Personality changes
- Decreased libido and impotence in men
- Dryness of mouth on awakening
- Morning headache (in some patients)
- Automatic behavior with retrograde amnesia
- Hyperactivity in children
- Hearing impairment (in some patients)

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Risk factors 00:20:47

Risk Factors for Obstructive Sleep Apnea Syndrome

- Male gender
- Increasing age
- Menopause (women)
- Body mass index (≥25 is considered overweight, and 230 is
- considered obese)
- Increasing neck circumference (>17 inches in men and 16 inches
- in women
- Race (increased prevalence in Pacific Islanders, Mexican
- Americans, and African Americans)
- Alcohol
- Smoking
- Increasing drug use
- Familial aggregates
- Nasal allergies or congestion
- Endocrine diseases
- Dysautonomia
- Disorders with craniofacial abnormalities

Physical findings 00:22:55

- Obesity in the majority of patients (70%)
- Increased body mass index (body weight in kg/height in m^2):
- overweight ≥25-29; obese ≥30
- Increased neck circumference (>17 inches in men and >16 inches in women)
- In some patients:
- Large edematous uvula
- Low-hanging soft palate
- Large tonsils and adenoids (especially in children)
- Retrognathia
- Micrognathia
- Hypertension
- Cardiac arrhythmias
- Evidence of congestive heart failure

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Pathophysiological events	Intermediate mechanisms	Subclinical consequences	Disease end points
• Intermittent hypoxemia • Sleep fragmentation • Large intrathoracic pressure swings	• Oxidative stress • Sympatric nervous system activation • Hypothalamic pituitary	• Elevated blood pressure • Metabolic dysregulation • Systemic inflammation	• Hypertension • Type 2 diabetes • Coronary heart disease • Cerebrovascular disease

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	adrenal activation • Increased cardiac preload and after load	• Endothelial dysfunction • Myocardial dysfunction	• Arrhythmia • Heart failure

OSAHS (Obstructive sleep apnea hypopnea syndrome)

- Apnea: Cessation of breathing for >10 seconds
- Hypopnea: Air flow limitation ≥30%

  Increases O2 saturation by 3%
- Based on AHI (Apnea – hypopnea index), Divided into
- AHI: No apnea/hypopnea per hour of sleep

  ↓

  - Mild: 5-14
  - Moderate: 15-29
  - Severe: ≥30

Epworth sleepiness scale	
Eight situations	**Scores**
Sitting and reading	-
Watching television	-
Sitting in a public place (e.g. a theater or meeting)	-
Sitting in car as a passenger for an hour without a break	-
Lying down to rest in the afternoon	-

Sitting and talking to some	–
Sitting quietly after a lunch without alcohol	–
In a car while stopped for a few minutes in traffic	–
Scale to determine the total scores: 0, would never doza; 1, slight chance of dosing; 2, moderate chance of dozing; 3, high chance of dozing	

Stanford sleeping scale	
Scale rating	**Degree of sleepiness**
1	Wide awake, active, and alert
2	Awake and able to concentrate but not functioning at peak
3	Relaxed awake and responsive but not fully alert
4	Feeling a little foggy
5	Difficulty staying awake
6	Sleepy prefer to lie down
7	Cannot stay awake; sleep onset is imminent

Diagnosis 00:33:35

- Gold standard – Polysomnography
  ↓
  - EEG
  - EOG

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- Nasal flow monitor
- Belts thoracic and abdominal
- EMG
- Spo2
- ERG

Fig: 7

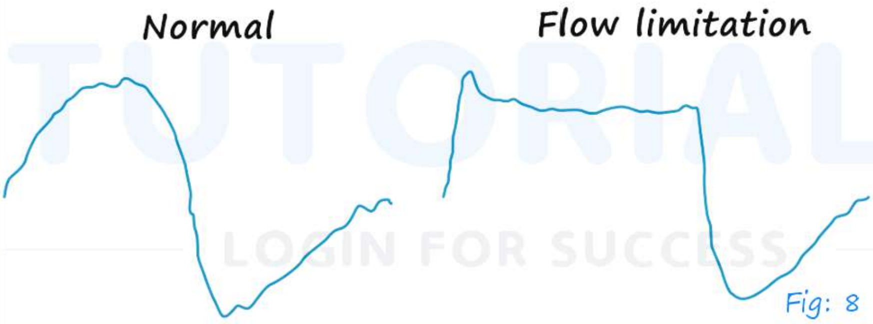

Fig: 8

- In OSA → Early inspiratory peak

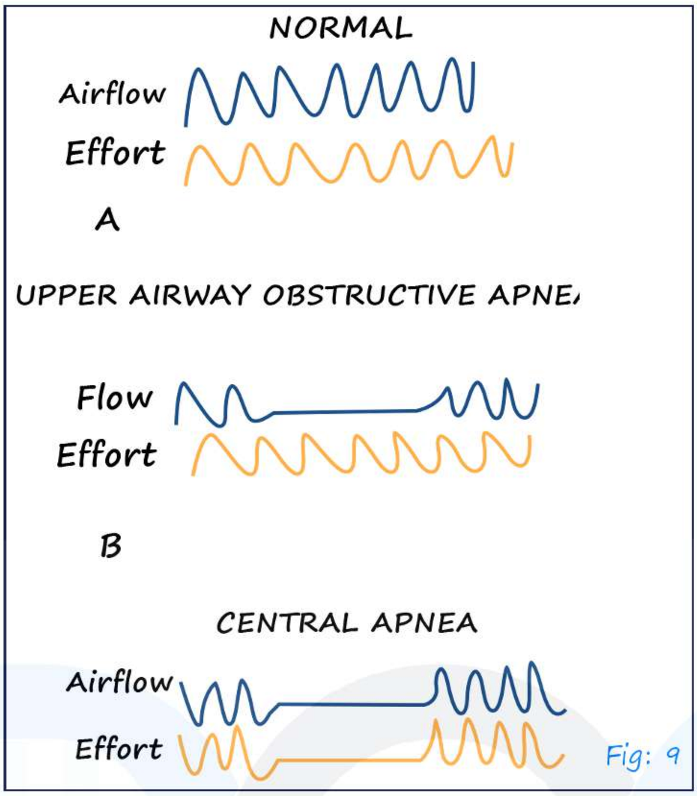

Fig: 9

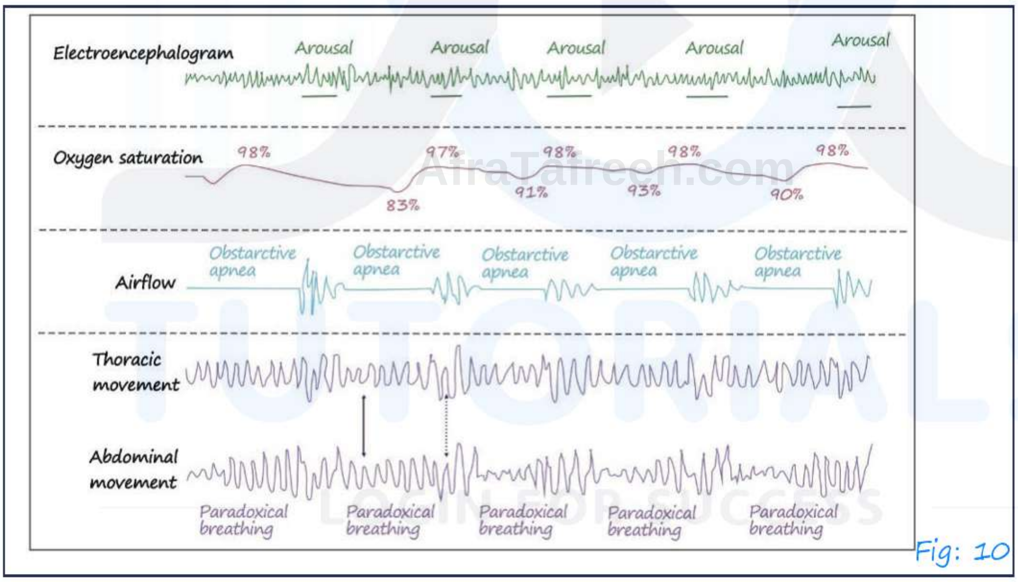

Fig: 10

Treatment 00:41:49

1.Behavioral and lifestyle modification

↓

- Weight reduction
- No Alcohol near bed time
- No smoking
- No drugs

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2.CPAP

Fig: 11

- Splint the airways open
- Best evidence

3.Oral airway devices

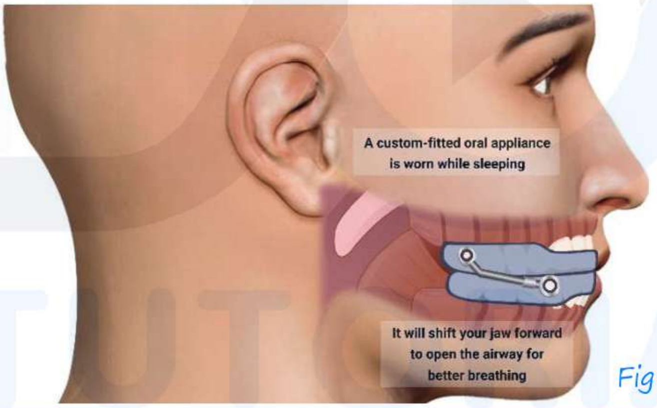

Fig: 12

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4.Surgery → Uvulopalatopharyngoplasty.

CLASSIFICATION OF SEIZURES, EPILEPSY AND EPILEPSY SYNDROME

Introduction 00:00:22

- Term seizure is derived from a Latin word "sacire" – to take possession of
- Seizure: - definition given by International League Against Epilepsy (ILAE)
  - Defines seizure as transient occurrence of symptoms/signs due to abnormal excessive synchronous neuronal activity in brain
- Convulsion: - motor manifestation of seizures
- Epilepsy: -
  - Defined as 2 or more unprovoked seizures that last 24 hours apart
  - A person has enduring predisposition to develop recurrent seizure
  - Recent: - even 1 unprovoked seizure

    +

    60% chance of developing active seizures in the next 10 years

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Classification of seizures (latest 2017 ILAE criteria)

00:08:58

- Partial
  - simple
  - complex
- Generalized

- Currently, there is no entity called partial seizures (since 2010)
- Simple partial seizures referred to as focal seizures without dyscognitive features
- Complex partial seizures referred to as focal seizures with dyscognitive features

• Now, no entity called dyscognitive features

Basic version:

Focal onset	Generalized onset	Unknown onset
Aware | impaired awareness	**Motor** - Tonic-clonic - Other motor **Nonmotor** (absence)	**Motor** - Tonic-clonic - Other motor **Nonmotor** (absence)
Motor onset Nonmotor onset		Unclassified
Focal to bilateral tonic-clonic		

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Expanded version:

Focal onset	Generalized onset	Unknown onset
Aware | impaired awareness	**Motor**	**Motor**
Motor onset	Tonic-clonic	Tonic-clonic
Automatisms	Clonic	Epileptic spasms
Atonic	Tonic	**Nonmotor** (absence)
Clonic	Myoclonic	Behavior arrest
Epileptic spasms	Myoclonic-tonic-clonic	
Hyperkinetic	Myoclonic – atonic	Unclassified
Nonmotor onset	Atonic	
Autonomic	Epileptic spasms	
Behavior arrest	**Nonmotor (absence)**	
Emotional	Typical	
Sensory	Atypical	
Focal to bilateral tonic-clonic	Myoclonic	
	Eyelid myoclonic	

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- Focal seizures: -
  - Seizures originates from neuronal Network in one cerebral hemisphere
- Generalized seizures: -
  - Seizures originated from neuronal network in both cerebral hemispheres
- Automatism: -
  - Apparently purpose less movements in more or less coordinated manner, repetitive movements
  - Lip smacking, swallowing, bed picking

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- Hyperkinetic: - previously hyper motor and violent movement
- Autonomic features
  - Increase BP
  - Tachycardia
  - Piloerection
- Behavioral arrest: - sudden stare
- Simple partial seizures: - focal with preserved awareness
- Complex partial seizures: - focal with impaired awareness

↓

Aura, Arrest, Automatism, Amnesia

- Aura can be visual, olfactory (like rotten egg smell), sensory
- Abdominal Aura seen in temporal lobe seizures
- Focal seizures
  - Frontal
  - Temporal → medial and lateral
  - Parietal
  - Occipital

Focal with preserved awareness - Patient aware of seizures

1. Jacksonian march: - seizures initially develop in fingers and slowly
2. TODDs PALSY: -

- Weakness of limb followed by seizure of the particular limb
- Weakness lasts for 24-36 hours
- Occurs due to neuronal exhaustion

3. Epilepsia partialis continua: - focal seizures occurring as status

- Myoclonic – tonic – clonic seizures are seen in juvenile myoclonic epilepsy
- Myoclonic atonic seen in Doose syndrome
- Generalized tonic – clonic seizures

↓

Most common seizures associated with metabolic disturbances

i. Prodromal stage

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ii. Tonic stage

- Tonic – clonic → LOC ⊕ , urinary incontinence, tongue bite
- When there is tonic seizure of laryngeal muscles

↓

Loud sound produced (Ictal cry)

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iii. Post ictal confusion phase

Absence seizure (Typical) 00:48:22

- Abrupt onset and abrupt offset
- Short lasting (seconds)
- Loss of consciousness ⊕

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- No loss of postural control
- No post ictal confusion
- Hundreds of seizures may occur in a day
- Day dreaming
- Poor scholastic performance
- Subtle motor manifestations → eye blinking, chewing
- Common manifestation of epilepsy syndromes like

  a) Childhood absence epilepsy

  b) Juvenile absence epilepsy
- EEG: – 3 H_z spike and wave pattern

Atypical absence seizures 00:53:40

- Onset and offset are less dramatic compared to typical
- Post ictal confusion ⊕
- MRI may show abnormalities
- Jeavan's syndrome characterized by eyelid myoclonia

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Classification of epilepsy

- Focal
- Generalized
- Combined focal + generalized
  - ↓ Lennox gestact syndrome (LGS)
- Unknown onset

Classification for epilepsy syndromes

- Constellation of symptoms (epilepsy – dominant features)
- Combination of clinical features

  EEG

  Imaging

  Genetic testing
- Genetic generalized epilepsy
  - Childhood absence epilepsy
  - Juvenile absence epilepsy
  - Juvenile myoclonic epilepsy
  - Genetic GTCS type epilepsy
- Lennox Gastaut syndrome
- Medial temporal lobe epilepsy syndrome.

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BASICS OF EEG

Introduction 00:00:16

- Scalp EEG – Electrodes on scalp surface, picks up electrical potentials

  Electrical potentials – sum of EPSP + IPSP

  EPSP – Excitatory Post Synaptic Potential

  IPSP – Inhibitory Post Synaptic Potential

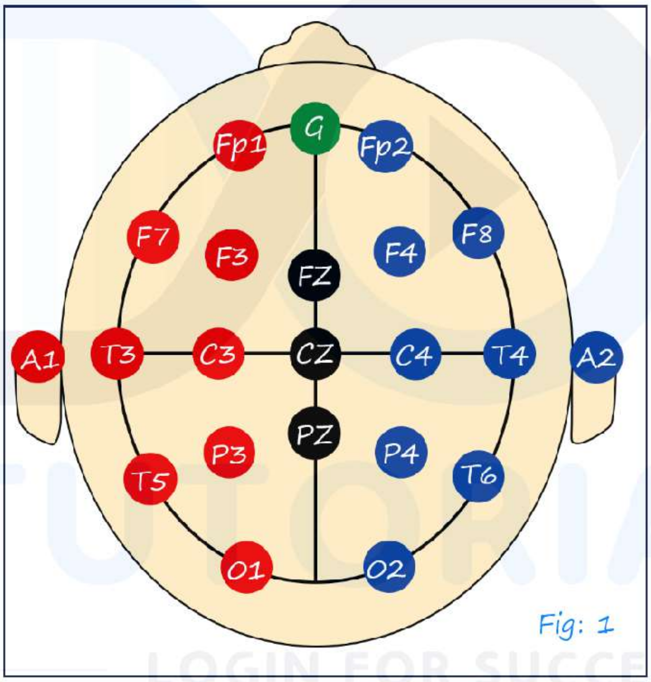


Fig: 1

Nasion

Preauricular points ↔ pre-auricular points

Inion

- Electrodes are placed in 10-20 system

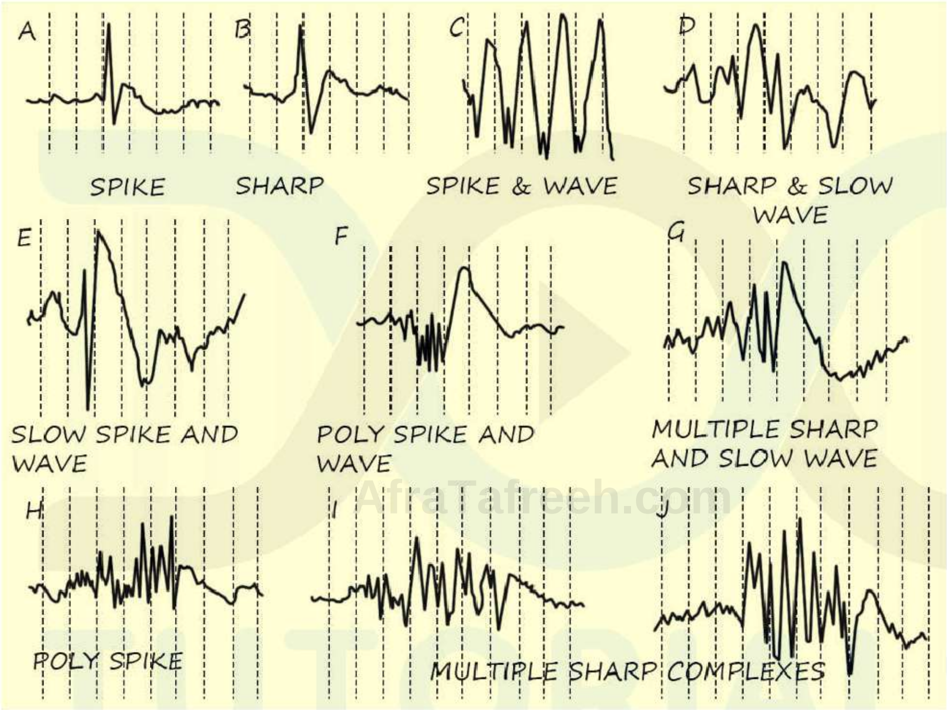
  FP_1 – Frontopolar 1

  19+2 = 21 Electrodes

- First human EEG recording was done by Hans Berger

Normal waves

- Beta → 13-40 Hz
- Alpha → 8-13 Hz → predominant normal background rhythm
- Theta → 4-7 Hz
- Delta → <4 Hz



- Spike – Pointed deflection with a duration of 20-70 ms
- Sharp – Duration 70-200 ms

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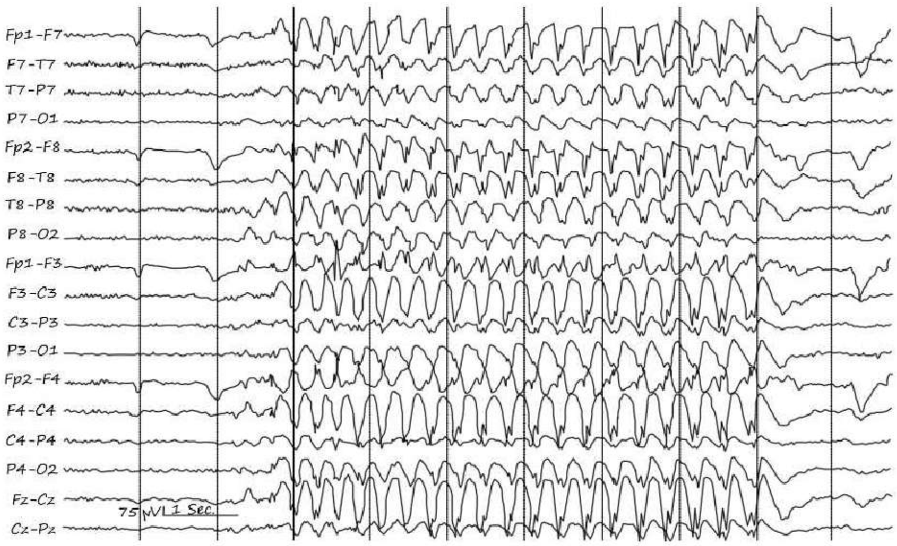


- Individually, each one is called a channel
- Arrangement of channels together is called montage
- Normally, look for ground activity → parietooccipital activity → alpha rhythm
- EEG Epoch – 10 seconds

  Each is 1 second
- 3 H_z spike & wave pattern

  ↓

  Absence seizures

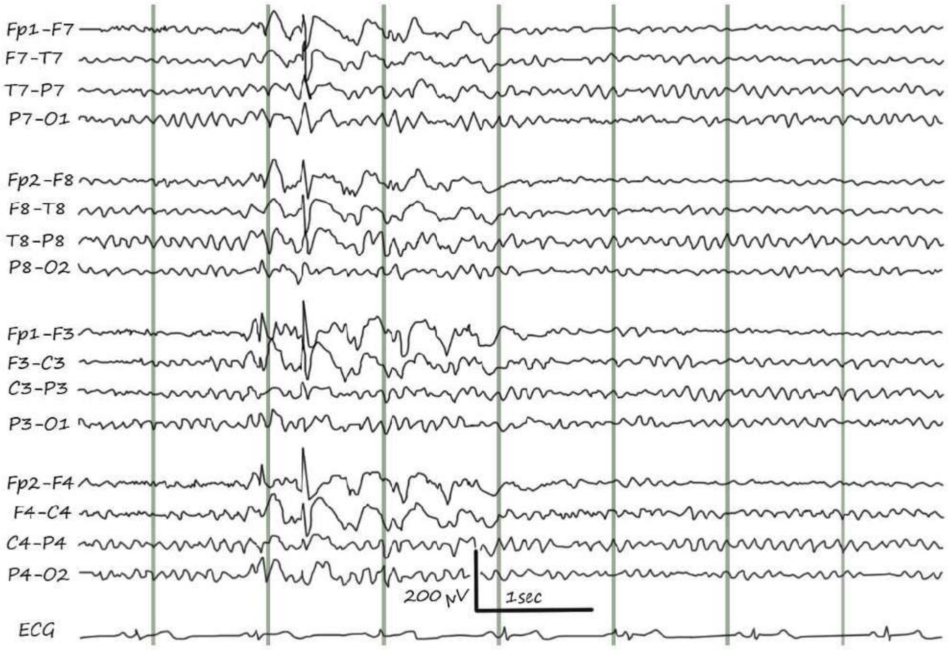
Uses of EEG 00:17:54

Diagnosis

i. Epileptiform or non-epileptiform

ii. Focal or generalized

iii. Epilepsy syndromes



Treatment aspect

i. NCSE – Non-Convulsive Status Epilepticus

Prognostication

↓

EEG – Abnormal → chance of recurrence ⊕

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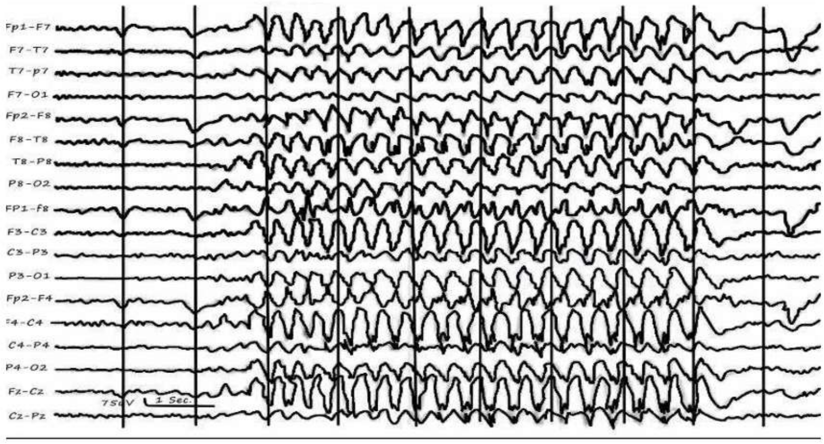
EPILEPSY SYNDROMES

Childhood Absence Epilepsy 00:00:30

- Also known as petit mal epilepsy – children
- Also referred to Pyknolepsy, Greek – 'pyknos' – crowded
- Age: 4-10 years
- Females > Males
- Genes: CACNA 1A
  GABAR G2
  GABAR G3
- Clinical features: Typical absence seizures
  - Day dreaming
  - Duration: 10-15 seconds
  - Eye blinking
  - Automatism
  - No post ictal confusion
  - No loss of postural control
- Diagnose:
  EEG: 3 H_2 spike and wave pattern



↓

Bilateral synchronous & symmetric

→ Ask the patient to hyperventilate → triggers absence seizures

- Treatment:

  Drugs acting on T Type calcium channel

  1.DOC: Ethosuximide

  2.Valproate

  3.Clonazepam

  4.Lamotrigine

Juvenile Absence Epilepsy 00:08:50

a. Age: 10-14 years

b. Absence seizures – less clustered

c. GTCS +

d. Treatment: Ethosuximide, Valproate

Juvenile Myoclonic Epilepsy (JME) 00:10:00

a. Age: 12-18 years

b. Janz syndrome / Impulsive petit mal

c. Clinical features: Myoclonic seizures (100% cases)
GTCS
Absence seizures

d. Genetics: Polygenetic → most prominent – GABAR A_1

e. Treatment: DOC: Valproate
Levetiracetam
Lamotrigine

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Phenytoin
Carbamazepine.
Oxcarbazepine
Gabapentin
Vigabatrin

} C/I in JME

f. EEG: 4–6 H_z spike/ poly spike and wave pattern

Lennox Gastaut Syndrome (LGS) 00:16:08

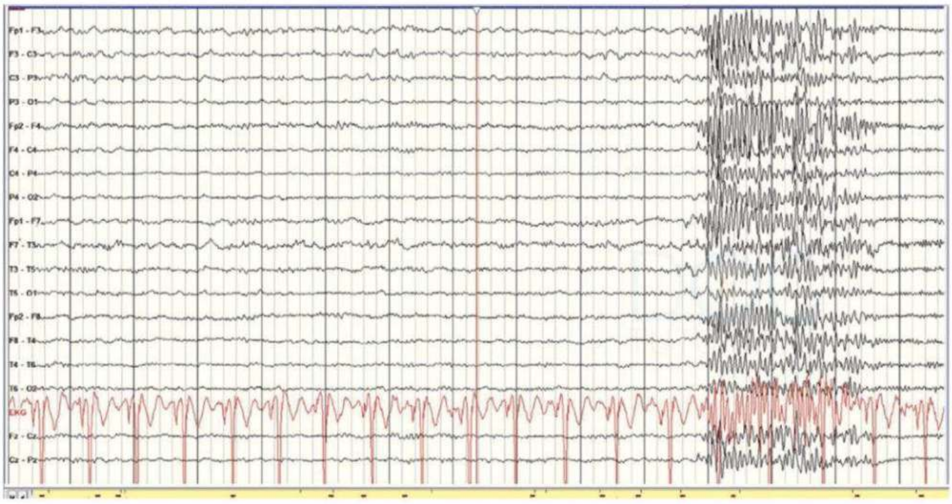
- Children
- Age: 1st decade – average age – 8 years
- M > F
- Triad of

1.Multiple seizure types

GTCS, Atonic, Atypical absence seizures

2.EEG: Slow spike and wave pattern (<2.5 H_z)

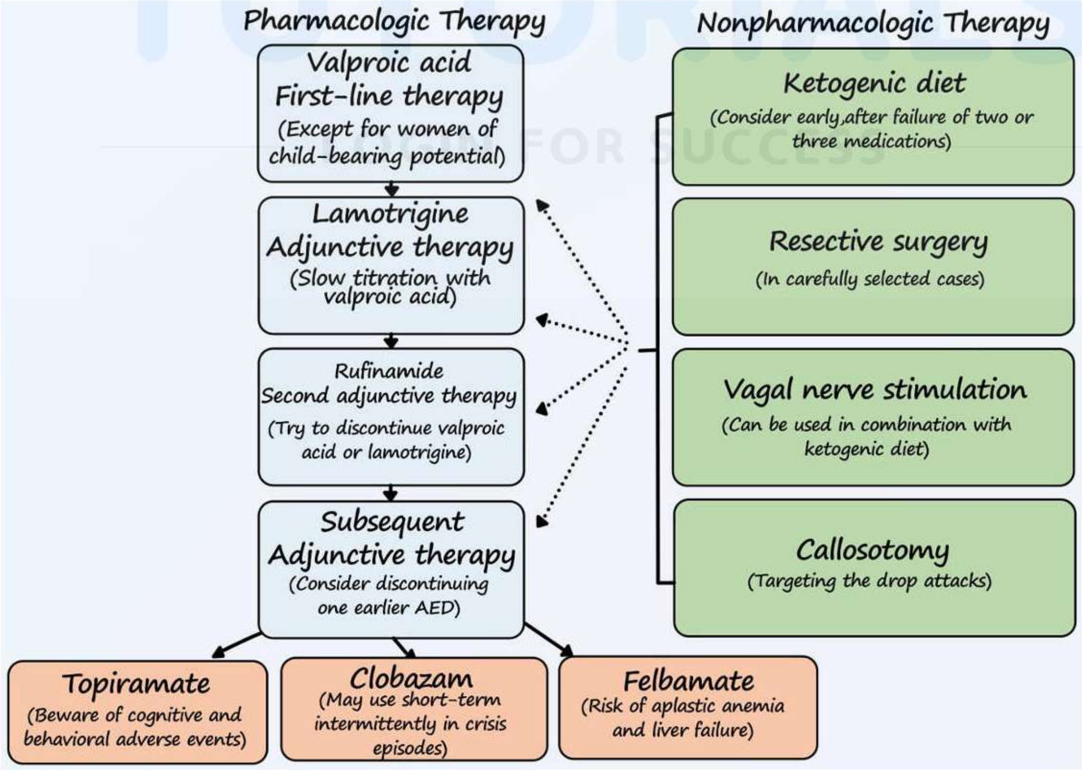
3.Cognitive dysfunction (subnormal intelligence)



↓

Generalised Paroxysmal fast activity

- Etiology : varied
  - Structural problems (focal cortical dysplasia)
  - Hypoxia
  - Denovo mutation
- Treatment:



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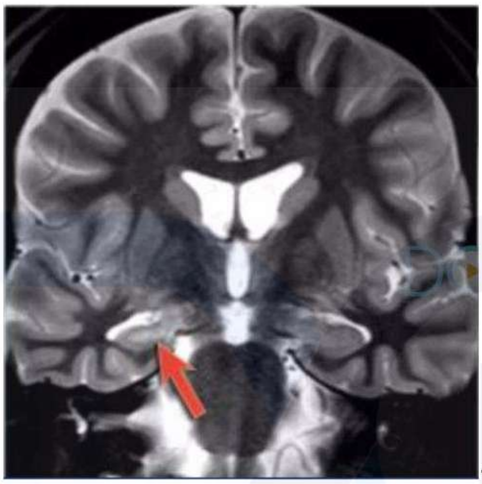
Mesial Temporal Lobe Epilepsy 00:24:28

- Medial temporal lobe epilepsy
- Most common epilepsy syndrome with focal seizures and impaired awareness
- Refractory epilepsy



→ coronal T_2 image

Small, atrophic and gliotic hippocampus

Fig: 1

- Treatment: Antiepileptics

↓

not responding → Surgery

↓

Amygdalo hippocampectomy

CAUSES OF SEIZURES

Causes of seizures 00:01:23

Causes of seizures	
Neonates (<1month)	Perinatal hypoxia and ischemia Intracranial hemorrhage and trauma CNS infection Metabolic disturbances (hypoglycemia, hypocalcemia, hypomagnesemia, pyridoxine deficiency) Drug withdrawal Developmental disorders Genetic disorders
Infants and children >1month and <12years)	Febrile seizures Genetic disorders (metabolic, degenerative, primary epilepsy syndromes) CNS infection Developmental disorders Trauma
Adolescents	Trauma Genetic disorders Infection Illicit drug use Brain tumor Autoantibodies
Young adults (18-35 yrs)	Trauma Alcohol withdrawal Illicit drug use Brain Tumor Autoantibodies (Autoimmune epilepsies / encephalitis)

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Oder adults (>35years)	Cerebrovascular disease Brain tumor Metabolic disorders (Uraemia, hepatic failure, electrolyte abnormalities, hypoglycaemia, hyperglycaemia) Alzheimer's disease and other degenerative CNS disease Autoantibodies

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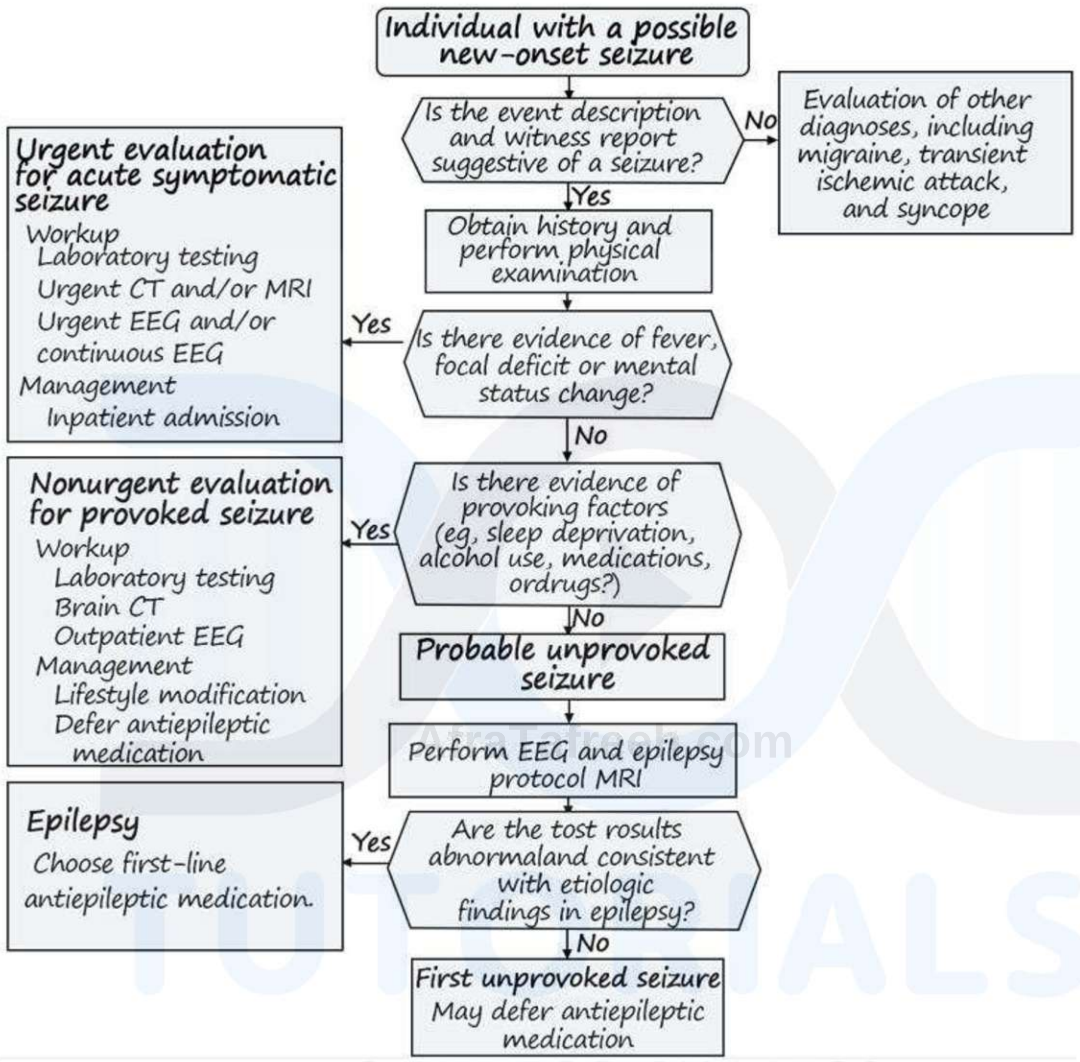
EVALUATION OF FIRST ONSET SEIZURES

Evaluation of new onset seizures 00:01:00



- Contrast imaging is must for meningeal enhancement
- Alcoholics → Rum fits and Delirium tremens
- Mesial temporal sclerosis

  ↓

  Small atrophic hippocampus bright in T2 sequence
- Structural causes
  - Large brain tumor
  - Metastasis

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- Tuberculoma
- Toxoplasma lesion

- Focal cortical dysplasia – high tesla MRI.

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SEIZURES VERSUS SYNCOPE

Seizures vs Syncope 00:00:24

Features that distinguish generalized tonic-clonic seizures from syncope

Features	Seizures	Syncope
Immediate precipitating	Usually none	Emotional stress Valsalva, orthostatic hypotension, cardiac etiologies
Premonitory symptoms	None or aura (example: odd odour)	Tiredness, nausea, diaphoresis, tunnelling of vision
Posture at onset	Variable	Usually, erect
Transition to unconsciousness	Often immediate	Gradual over seconds
Duration of unconsciousness	Minutes	Seconds
Duration of tonic or colic movements	30-60s	Never >15s
Facial appearance during event	Cyanosis fronting at mouth	Pallor

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Disorientation and sleepiness after event	Many minutes to hours	<5min
Aching of muscle after event	Often	Sometimes
Biting of tongue	sometimes	Rarely
Incontinence	Sometimes	Sometimes
Headache	Sometimes	Rarely

- Syncope: Transient reversible loss of consciousness due to cerebral hypoperfusion
- Tongue bite: Lateral aspect (Seizure) & Anterior aspect (Syncope)

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GENERAL PRINCIPLES IN MANAGEMENT OF SEIZURES AND EPILEPSY

General principles 00:00:18

1.Differentiating seizure from seizure mimics

2.Treatment has to be individualized

- Age group
- Co-morbidities
- Pregnancy
- Lactation
- Elderly

3.Treatment of underlying cause

- Herpes encephalitis – Acyclovir
- Hypoglycaemia
- Hyperglycaemia
- Hypocalcaemia

4.Look for predisposing factors

- Drugs default
- Sleep deprivation
- Drugs (cocaine, theophylline, levofloxacin)

5.Choosing the right antiepileptic

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Selection of Antiepileptic Drugs			
Generalised onset Tonic-clonic	Focal	Typical Absence	Atypical Absence, Myoclonic, Atonic
First line			
Lamotrigine Valproic acid	Lamotrigine Carbamazepine Oxcarbazepine Phenytoin Levetiracetam	Valproic acid Ethosuximide Lamotrigine	Valproic acid Lamotrigine Topiramate
Alternatives			
Zonisamide	Zonisamide	Lamotrigine	Clonazepam
Phenytoin	Brivaracetam	Clonazepam	Felbamate
Levetiracetam	Topiramate		Clobazam
Carbamazepine	Valproic acid		Rufinamide
Oxcarbazepine	Tiagabine		
Topiramate	Gabapentin		
Phenobarbital	Lacosamide		
Primidone	Phenobarbital		
Felbamate	Primidone		
	Felbamate		

- Focal seizures

  a. Carbamazepine
  b. Oxcarbazepine
  ] Less adverse effects favourable side effects
  c. Lamotrigine
  d. Lacosamide

- Elderly

  a. Hyponatremia → lamotrigine, phenytoin
  b. LFT deranged → levetiracetam

GTCS – Valproate

JME → ⎤
⎬ – valproate
LGS ⎦

6.Good follow up

- Serum level estimation of AED
- HLAB 1502 – SJS

7.Start low, go slow. - Carbamazepine

Start with one antiepileptic

8.Stopping the AED

↓

1-5 years seizure free

Higher chance of recurrence

- Family H/O epilepsy
- Status epilepticus
- Todd's palsy
- EEG – Abnormal
- Imaging – abnormal
- Neurological deficits

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DRUGS RESISTANT EPILEPSY

Drug resistant epilepsy

- Pharmaco-resistant epilepsy
  - Failure to achieve sustained seizures freedom in spite of 2 appropriately chosen and tolerated anti-epileptic drugs
  - Seizures free period of 1year or 3times the prior inter seizures interval which ever is longer

Treatment

- Surgical
  ↓
  Epilepsy surgery
  ↓
  Pre surgical evolution `
- Neuromodulation procedures
  ↓
  Vagal nerve stimulation
  Deep brain stimulation
  Responsive neurostimulation

STATUS EPILEPTICUS

- Neurocritical care society guidelines
- American epilepsy society guidelines

Definition 00:01:34

- 5 mins or more of continuous clinical or electrographic seizures

(or)

2 or more seizures without regaining consciousness in between

- SE
  a. Convulsive SE
  b. Non-Convulsive SE → EEG
- T_1 → 5 mins → very high probability of recurrent seizures
- T_2 → 30 mins → neuronal cell death & neuronal network disruption
- Early & aggressive therapy
- Refractory status epilepticus (RSE)
  - Continuous clinical / electrographic
  - seizures even after starting iv BZD + 2nd line agent
- super refractory status epilepticus (SRSE)
  - continuous clinical / electrographic seizures that occurs even after 24 hours of initiation of anaesthetic therapy

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- Etiopathogenesis of SE

  1.Infectious – viral encephalitis (most common)

  2.Metabolic & vascular etiology → elderly

  3.Autoimmune encephalitis

- Decrease GABA & increase NMDA

  ↓

  SE

- Management of status epilepticus

  1.Airway

  Breathing

  Circulation

  2.O_2 support

  3.Left lateral decubitus position

  4.Put a IV cannula

  Blood for RBS, S Ca^{++}, S Na^{+}

  5.Definitive management

  6.1st line – Benzodiazepines

  ↓

  i.v Lorazepam

  i.v Diazepam

  i.v Midazolam

  Alternatives: Rectal diazepam

  Intranasal/ buccal midazolam

  2nd line – Phenytoin

  Fosphenytoin

  Valproate

  Levetiracetam

Lacosomide

Initially give as loading dose to achieve steady state plasma concentration

Loading dose of phenytoin → 20 ml\kg in 100 ml Ns over

20 mins

↓

50 mg\min

50kg female → 50*20 = 1000mg

$\frac{1000mg}{50}$ = 20 minutes

Phenytoin extravasation leads to necrosis

Purple glove syndrome

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- 3rd line → Midazolam
  - Propofol
  - Phenobarbital
  - Thiopental
  - Ketamine
  - Isoflurane
- Midazolam → Hypotension
  - Tachyphylaxis
- Propofol → propofol infusion syndrome

  ↓

  - Hypotension
  - Metabolic acidosis
  - Lipidemia

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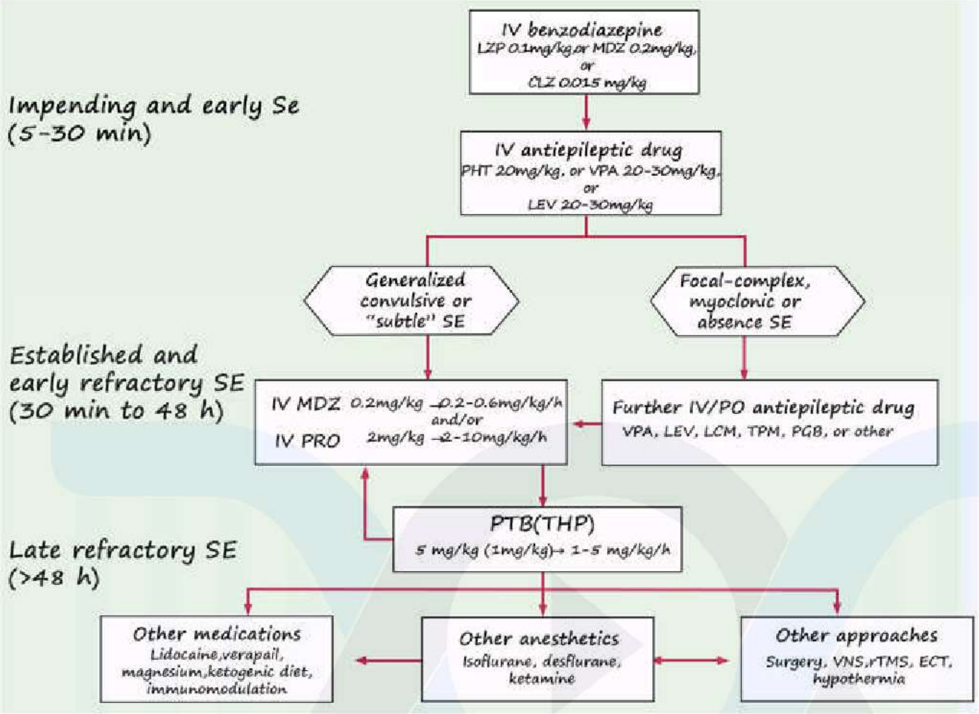
- Ketamine → does not cause cardiovascular compromise

Increase ICT & Increase IOP



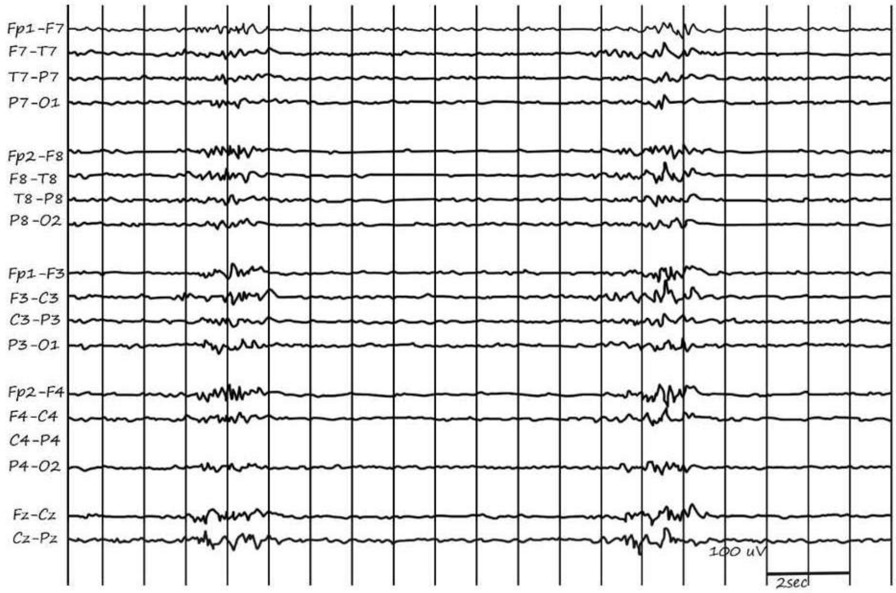
- Lorazepam: 0.1 mg/kg

  Max: 4mg I V

- Midazolam – max: 10mg I m
- Continuous EEG monitoring

↓

To achieve burst suppression



- Complications
  - SE
  - Drugs

- Initial stages of SE → sympathetic overactivity

  ↓

  ↑ BP

  ↑ Blood glucose

  ↑ Blood oxygen

- Soon it goes to decompensated stage

  ↓

  ↓ BP

  ↓ Blood glucose

  ↓ Blood oxygen

- Complications
  - SE
    ↓
    - Decompensated
    - Infections
  - Drugs
    ↓
    - Hypotension
    - Infection

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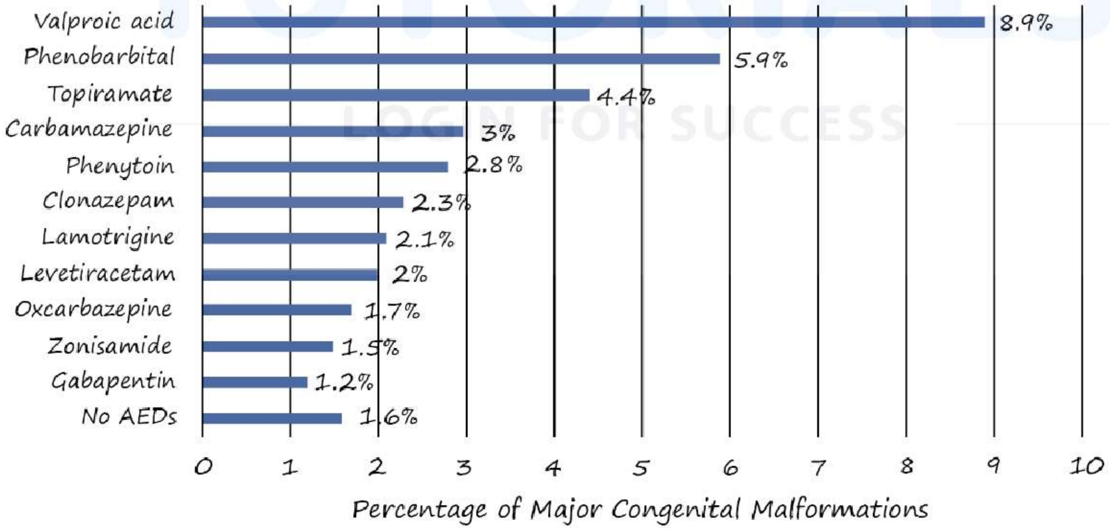
WOMEN AND EPILEPSY

Catamenial epilepsy 00:00:40

- Increased predisposition to seizures during menstrual cycle due to hormonal fluctuation
- Estrogen – Epileptogenic
- Progesterone – Anti epileptogenic
- Treatment
  - Clonazepam
  - Clobazam
  - Acetazolamide

Pregnancy 00:02:39

- 50% - Unaltered risk
- 30% - Increased risk
- 20% - Decreased risk
- Highest teratogenic risk – Valproate



- JME on valproate → Pregnant

↓

Comes for consultation at 5months

↓

Seizure free period of 2-3years

↓

Don't change antiepileptic

- JME patient planning to pregnant

↓

Shift to safer antiepileptic Levetiracetam

- JME with absence seizures (As dominant seizure type)

Planning pregnancy

↓

Lamotrigine

Lactation 00:12:32

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- Levetiracetam → Highest secretion into milk

Contraception

- Antiepileptic drugs causing contraceptive failure
  - Carbamazepine
  - Clobazam
  - Eslicarbazepine acetate
  - Oxcarbazepine
  - Phenobarbital
  - Phenytoin
  - Primidone
  - Rufinamide

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ARTERIAL SUPPLY OF BRAIN

- Anterior circulation
- Posterior circulation

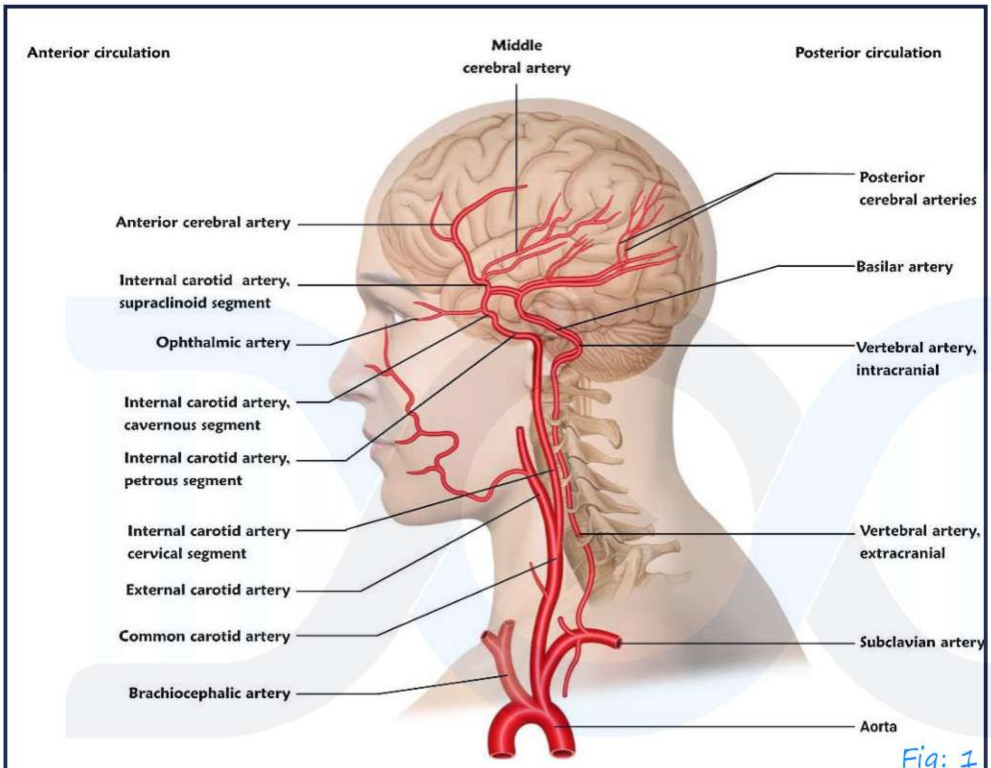

Fig: 1

- From aorta, 3 main branches
  - Brachiocephalic trunk
- Right CCA
- Right subclavian artery
  - Left subclavian artery

- Left common carotid artery

↓

At level of upper border of thyroid cartilage

ICA ECA

↓

Enters base of skill through carotid canal

↓

Enters middle cranial fossa via foramen lacerum

↓

Cavernous sinus

↓

At medial end of sylvian fissure

↓

2 terminal branches ACA and MCA

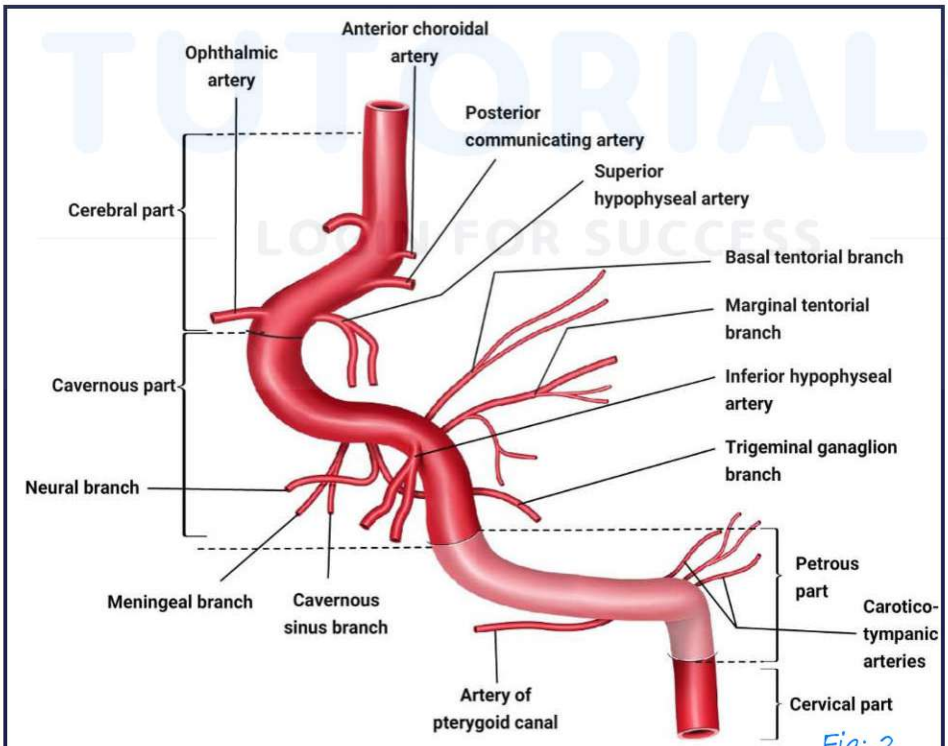

Fig: 2

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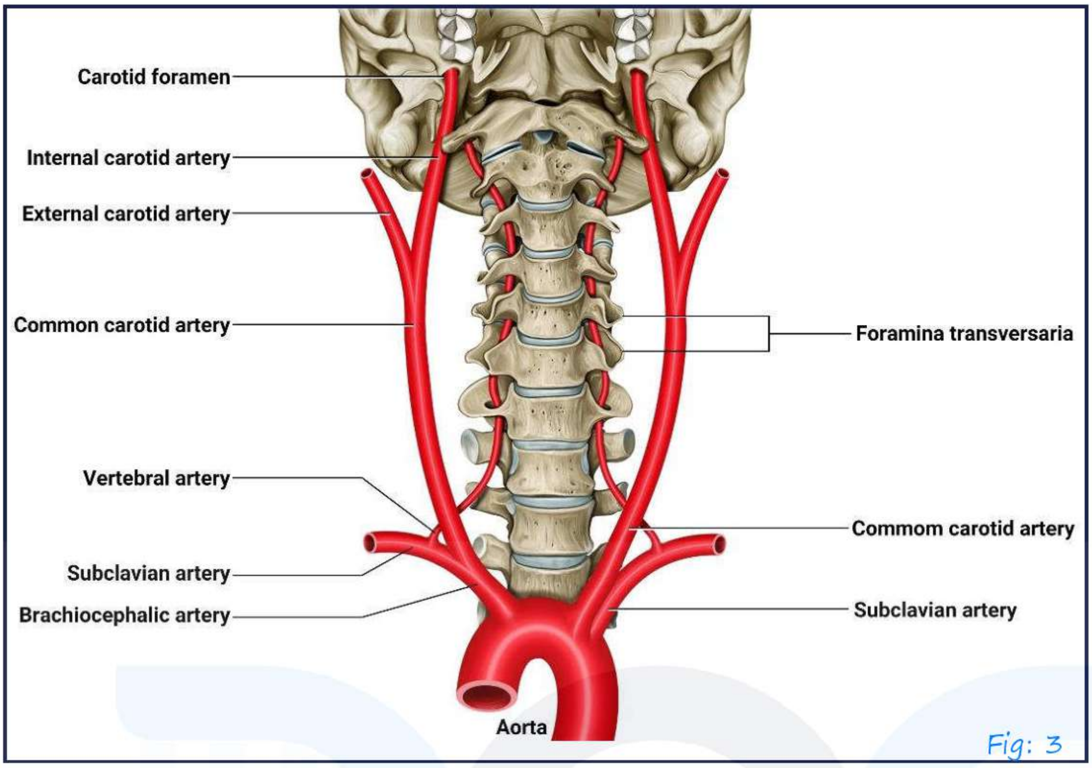

Fig: 3

Anterior circulation 00:11:14

- Anterior circulation (or) carotid circulation → cranial part of ICA and Its branches
- ECA – supplies musculoskeletal of head and neck
- Posterior circulation (or) vertebrobasilar circulation → vertebral artery + basilar with + PCA

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Circle of willis

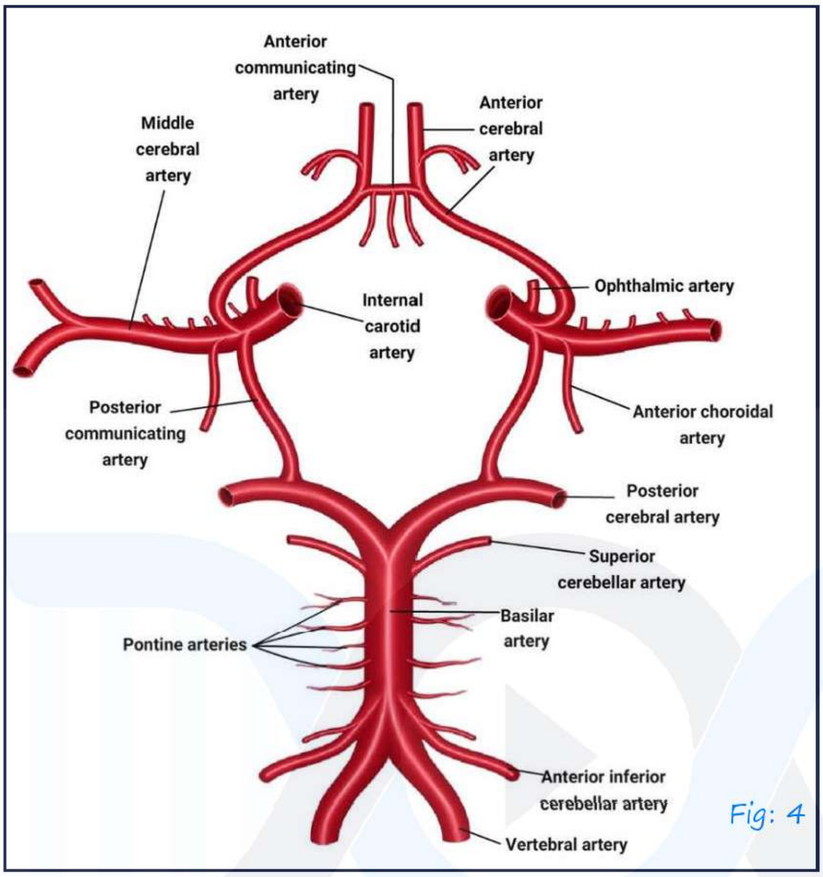

Fig: 4

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- Posterior communicating artery connects anterior circulation and posterior circulation.

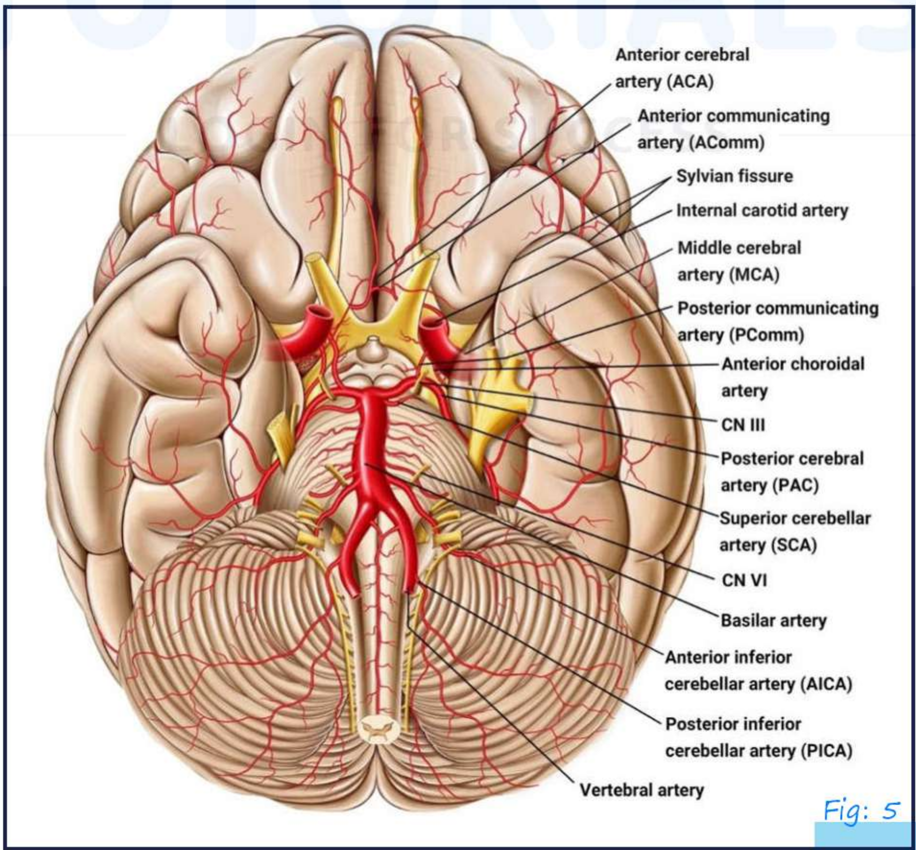

Fig: 5

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ACA

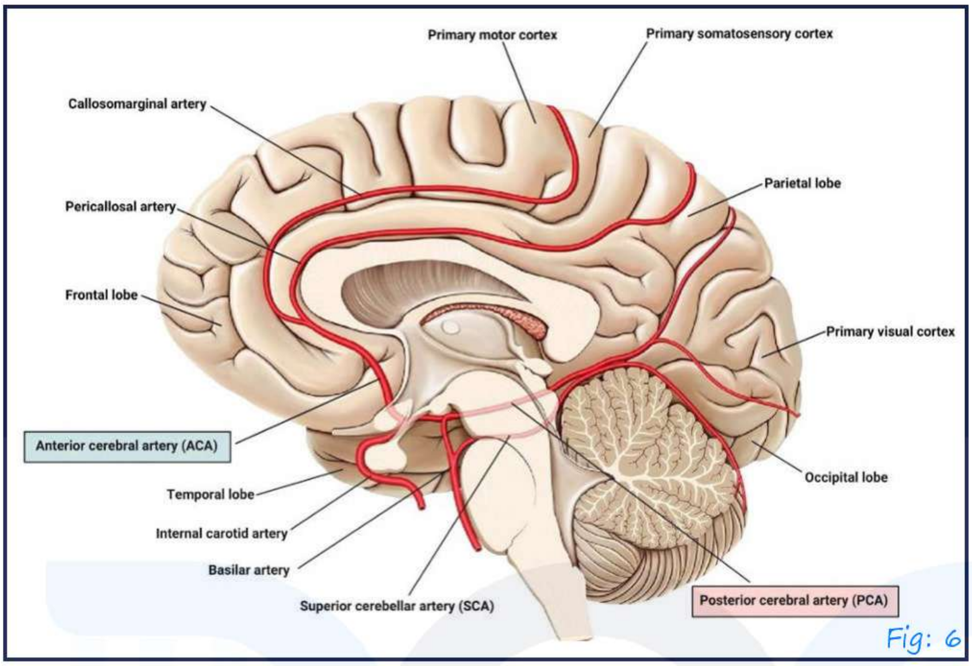

Fig: 6

- Anterior cerebral arteries are connected by anterior communicating artery
- Part of ACA before anterior communicating artery is pre-communal segment of ACA (A_1)
- Part of ACA after anterior communicating artery is post-communal segment of ACA (A_2)
- ACA → before winding around corpus callosum gives a branch
    - Callosomarginal artery
    - Pericallosal artery
- ACA → predominantly supplies medial part of cerebral hemisphere

MCA

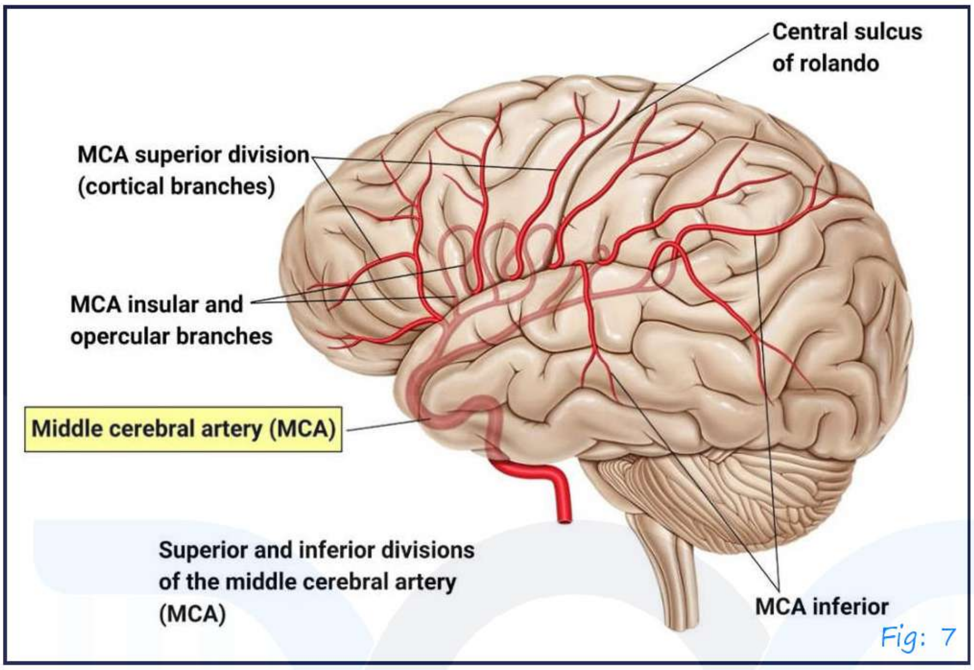

Fig: 7

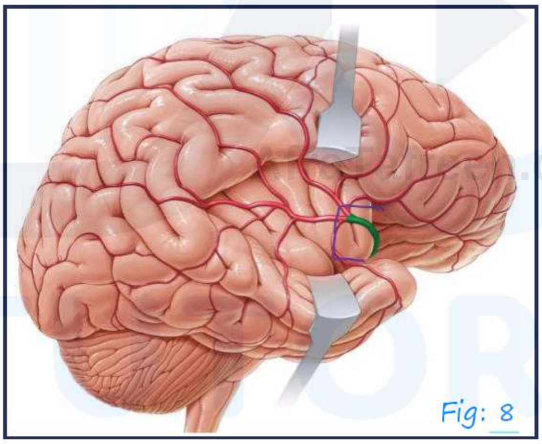
Fig: 8

- MCA divides in sylvian fissure into (Stem of MCA)

Superior division   inferior division

M_2 segment

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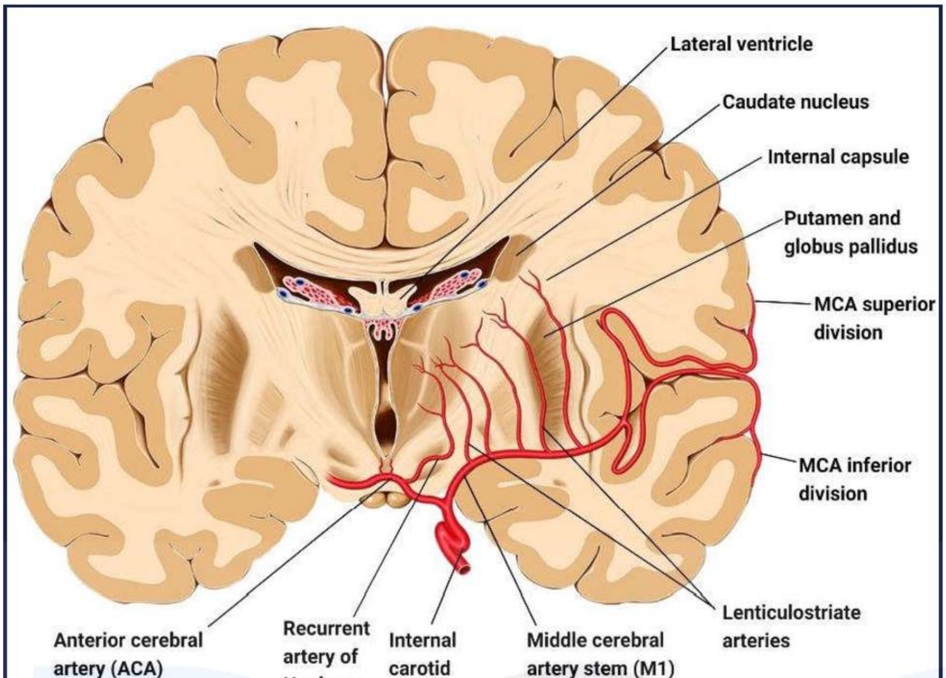


Fig: 9

- MCA (M_1) gives multiple small branches → lenticule – striate arteries
- ACA gives a recurrent branch → recurrent artery of Huebner

Lateral surface of cerebral artery of Huebner

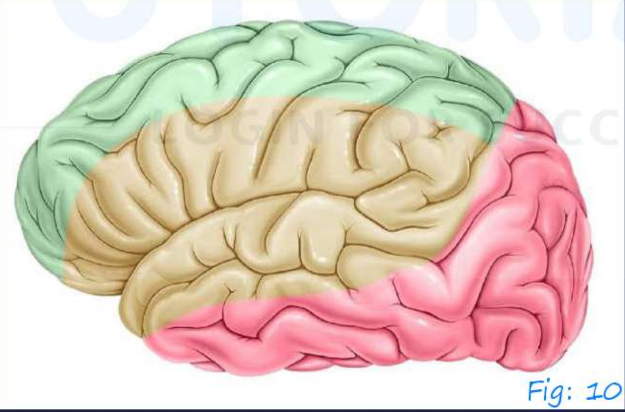


Fig: 10

- Predominant supply of lateral surface of cerebral hemisphere – MCA
  - Medial aspects of hemisphere → predominant supply → ACA

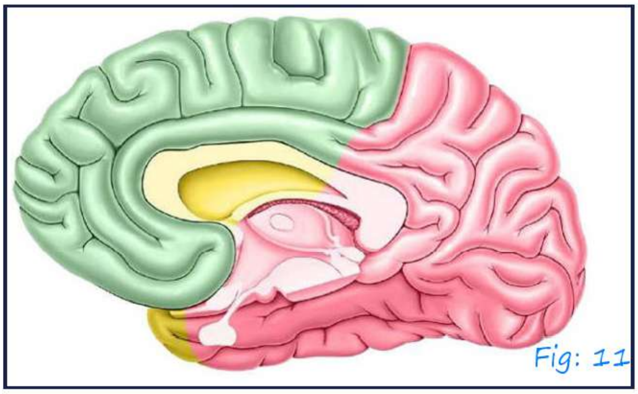


Fig: 11

- Inferior view → predominant supply – PCA

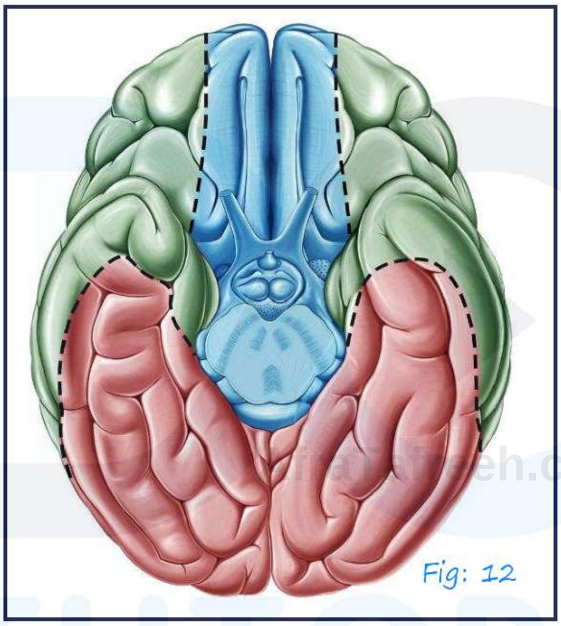
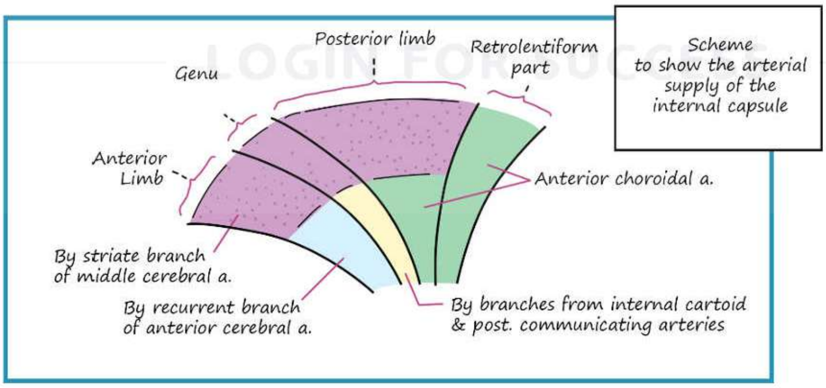


Fig: 12



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Axial section

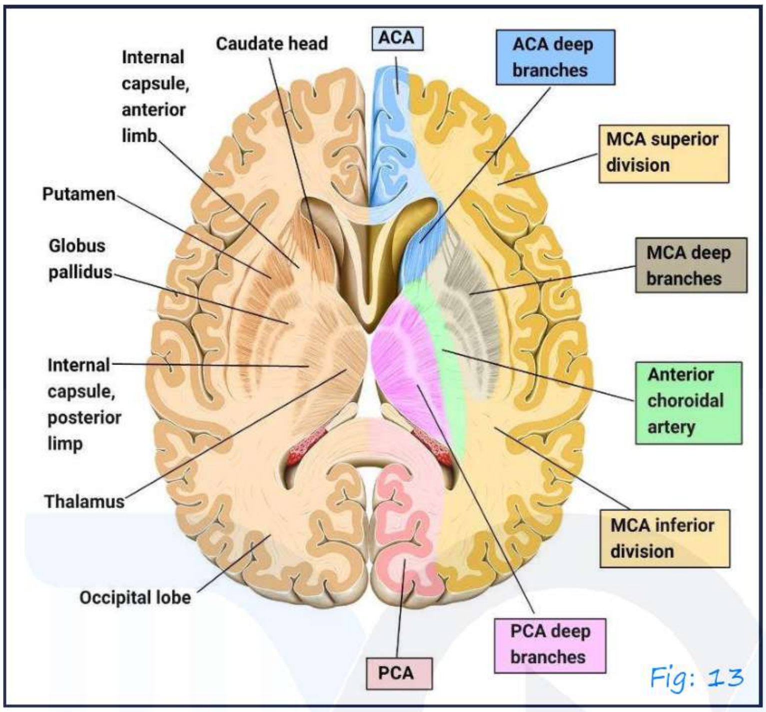

Fig: 13

Coronal view

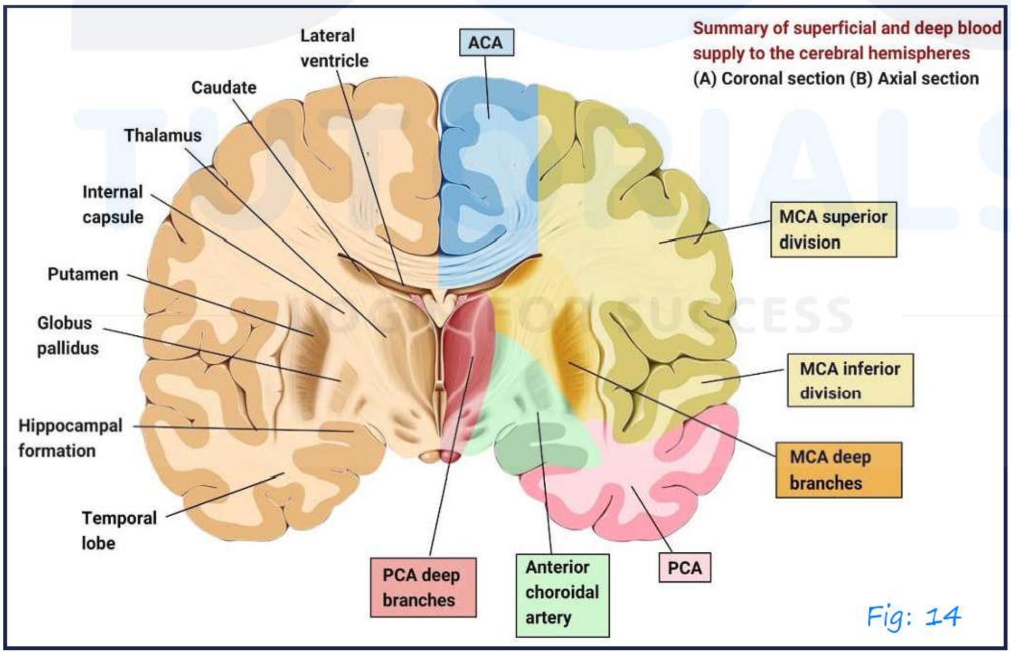

Fig: 14

Posterior circulation 00:32:26

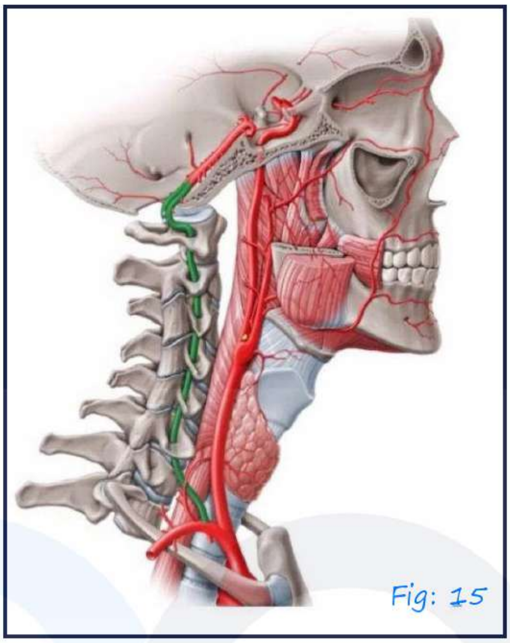

Fig: 15

- Vertebral artery is originating from subclavian artery
- Vertebral artery first enters foramen transversarium of C_6
  - Goes up subsequently and once it reaches foramen transversarium of C_2 → winds around and pierces dura and then gives branch to basilar artery

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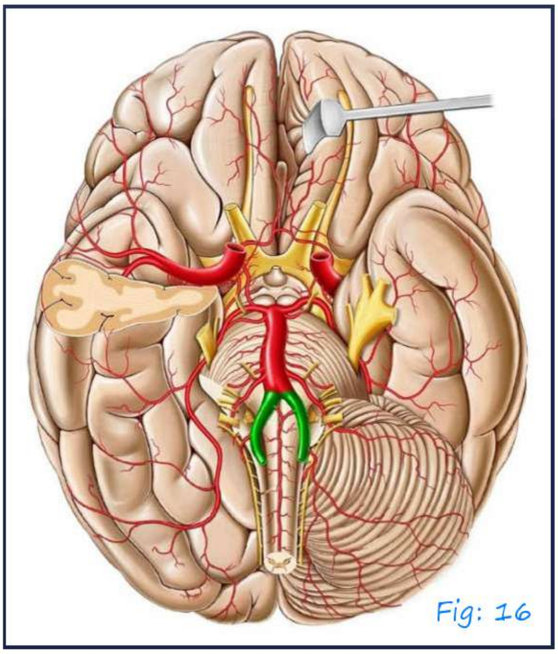

Fig: 16

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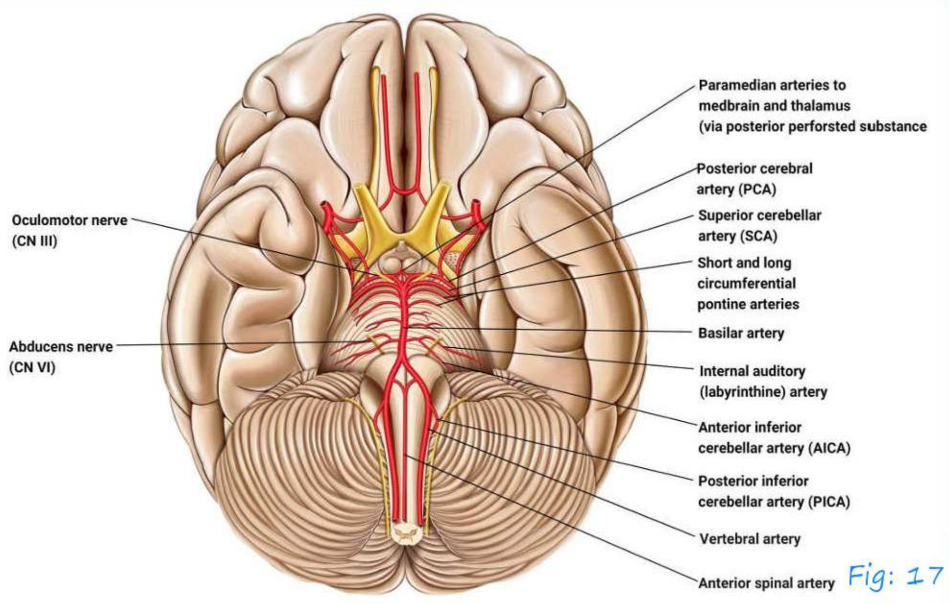

Fig: 17

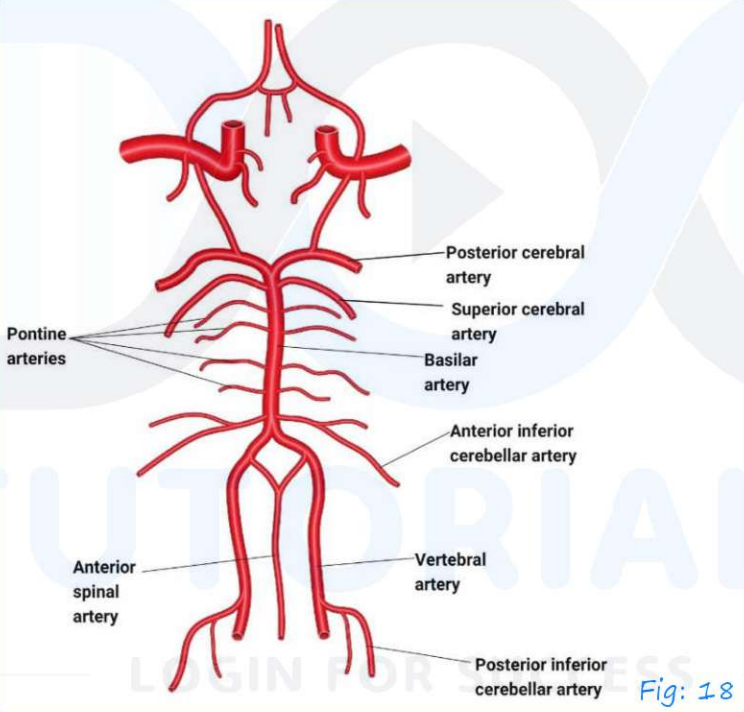

Fig: 18

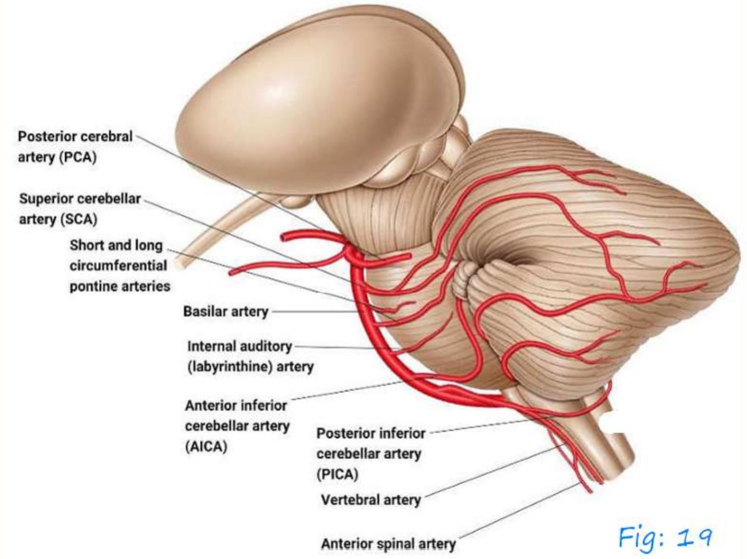

Fig: 19

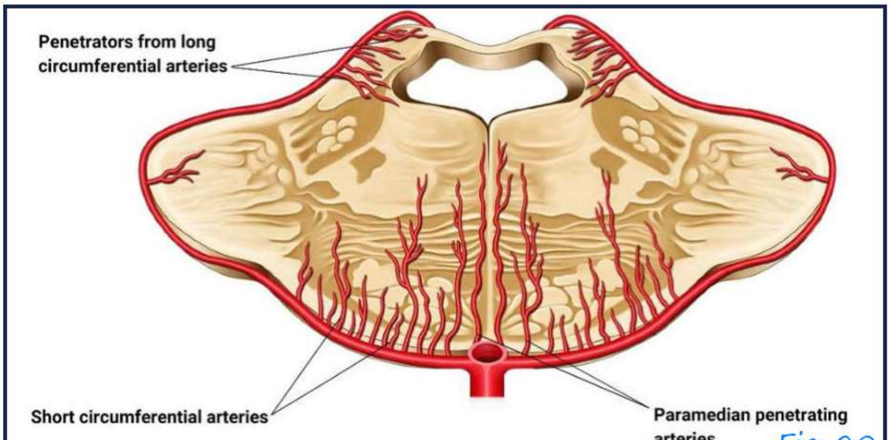

Fig: 20

- Long circumferential branches → SCA and ALCA

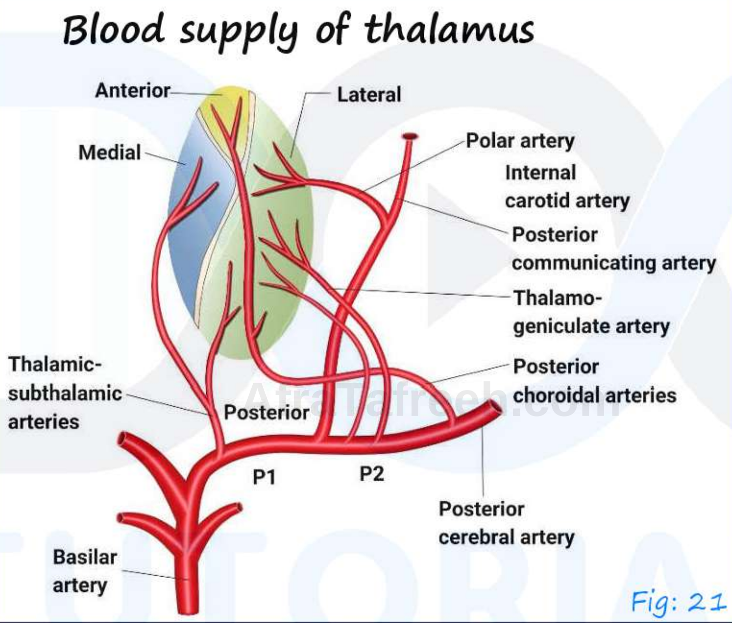

Fig: 21

Basal view

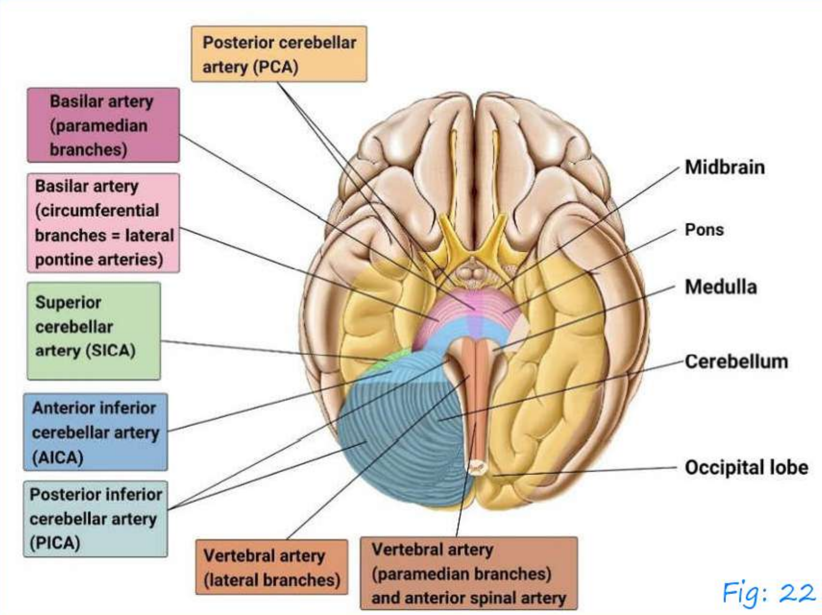

Fig: 22

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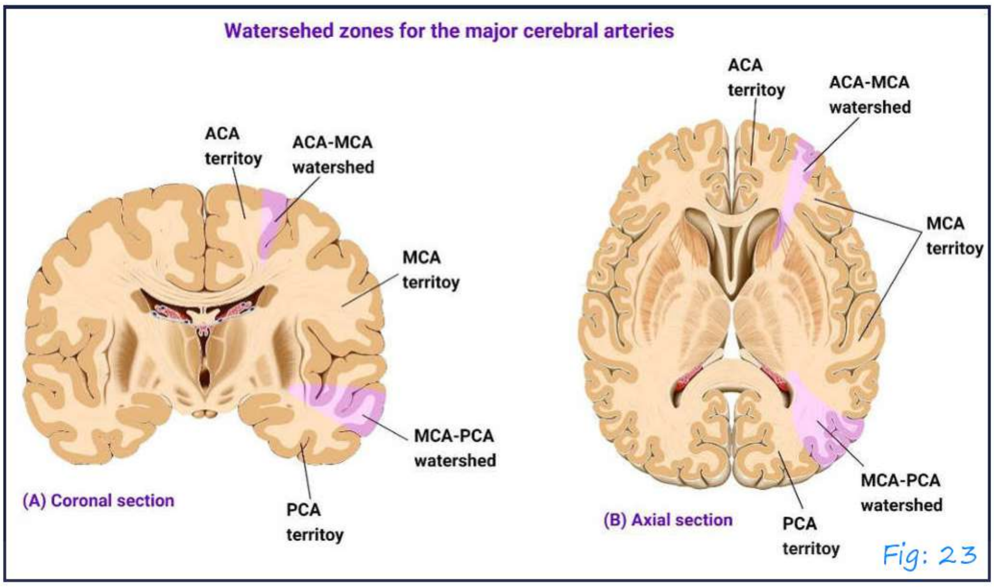

Fig: 23

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ETIOPATHOGENESIS OF STROKE

Definition of stroke 00:00:36

- STORKE /CVA
  - Abrupt onset focal neurological defect due to vascular cause which lasts for more than 24 hours / death within 24 hours
  - Focal neurological defect < 24 hours – Transient ischemic attack

Etiology of Stroke

- Modifiable risk factor
- non-modifiable risk factors

Risk factors for ischemic stroke

Non modifiable	Modifiable
Age	Arterial hypertension
Gender	Transient ischemic attacks
Race/ethnicity	Prior stroke
Family history	Asymptomatic carotid bruit/stenosis
Genetics	Cardiac disease Aortic arch atheromatosis Diabetes mellitus Dyslipidemia Cigarette smoking Alcohol consumption

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	Increased fibrinogen Elevated homocysteine Lack of physical activity Low serum folate Elevated anticardiolipin antibodies Oral contraceptive Obesity

Pathophysiology of Stroke 00:08:04

- Occlusion of blood vessel

↓

Cascade of events

↓

Cell death

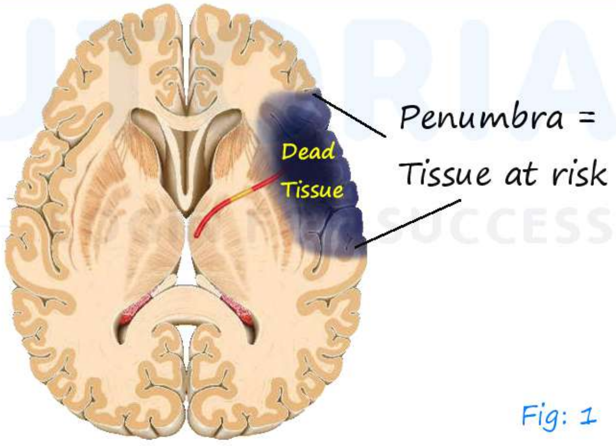

Fig: 1

→ Area at risk – penumbra

- Normal cerebral blood flow – 54ml/100g/min
- Occlusion → cerebral blood flow = 0

↓

Death of cerebral tissue within 4-10 mins

- Blood flow < 16-18 ml/ 100g/ min

↓

Cell death occurs in an hour

- Blood flow – 18-20 ml/100g/min → ischemia

↓

Prolonged → cell death

- Revascularization → I V thrombolysis
  Mechanical thrombectomy

↓

Saves penumbra

Cell death

- Necrosis
- Apoptosis

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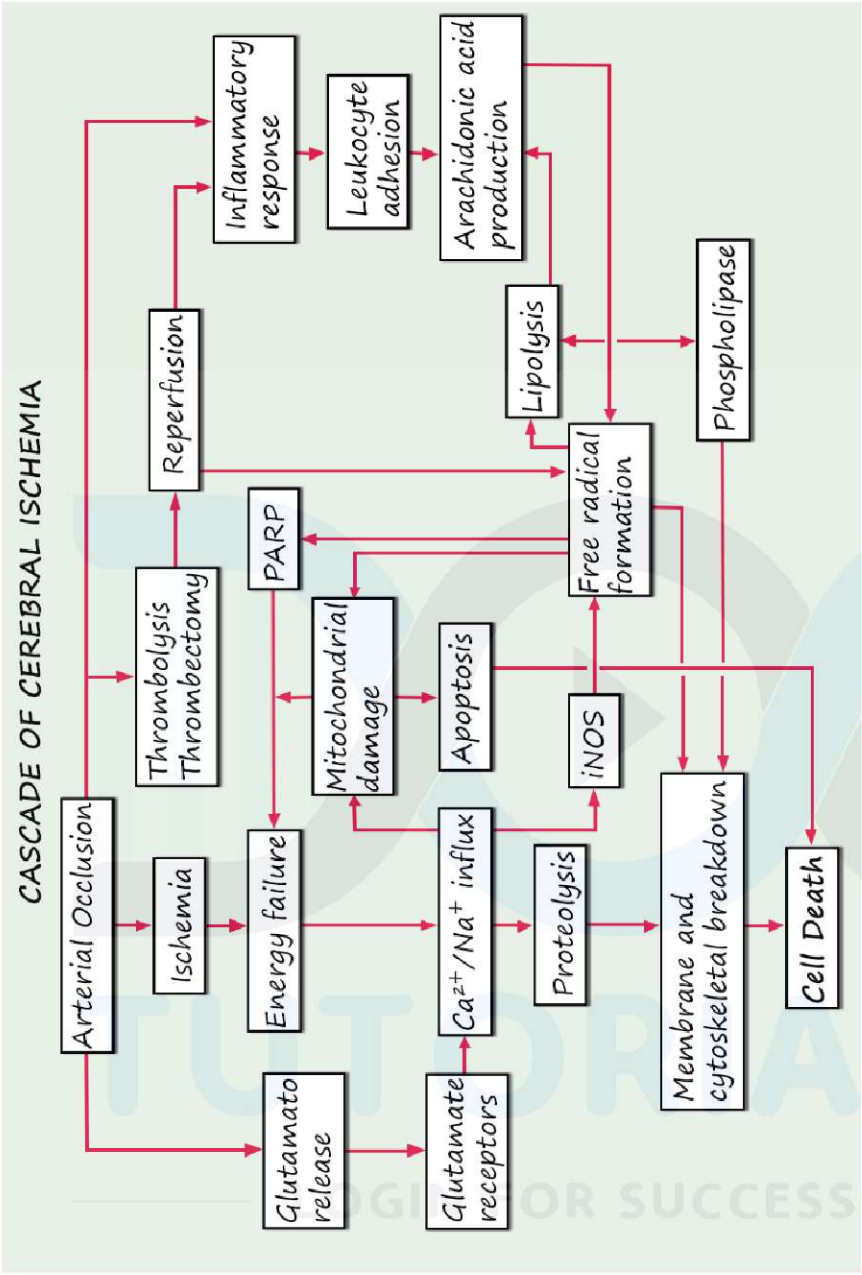
Key events



- Energy failure is due to failure of Na+/K+ ATP are pump
- i NOS – inducible nitric oxide synthase
- Stroke – multifactorial disease

SUBTYPES OF STROKE

Subtypes of Stroke 00:00:20

- Stroke
  - Arterial (Most common)
    - Ischemic
      - Thrombotic
      - Embolic
    - Haemorrhagic
  - Venous

- Most common of stoke – ischemic stroke / thromboembolic variety

Embolic > Thrombotic

Emboli → Cardiac

Artery to artery

Subtyping of Ischemic Stroke

Toast classification

1. Large artery stroke
2. Small vessel stroke
3. Cardio embolic stroke
4. Stroke of other determined etiology
5. Stroke of undetermined etiology

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Large Artery stroke 00:04:54

1.Large Artery Stroke

- Also referred to as large artery atherosclerosis as main pathology is atherosclerosis

↓

Intracranial / Extracranial large arteries

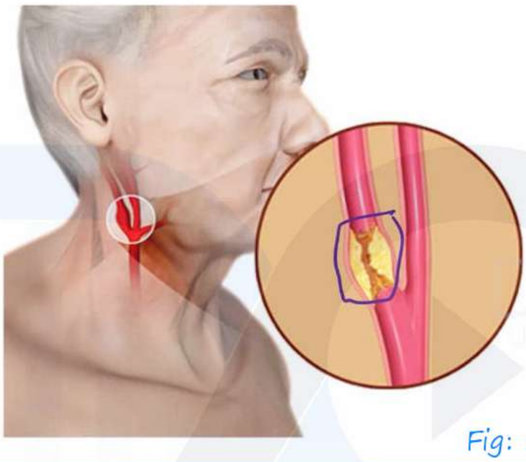

Fig: 1

- carotid bifurcation & proximal ICA

  vulnerable sites of extracranial atherosclerosis

→ Extracranial large artery atherosclerosis (LAA)

- Symptomatic
- Asymptomatic

→ Intracranial LAA

- Symptomatic
- Asymptomatic

→ ≥ 50% stenosis / occlusion of large vessel

↓

LAA

→ < 50% stenosis with significant ulceration / thrombosis

↓

LAA

→ Infracts of LAA > 2 cm diameter

→ LAA- M1 MCA, M2 MCA, A1 ACA, P1&P2 PCA

Small vessel disease 00:09:46

- Small vessels → 30-300 μm

↓

a. Lenticulostriate vessels
b. Thalamogeniculate artery
c. Perforators / penetrator vessels from basilar artery

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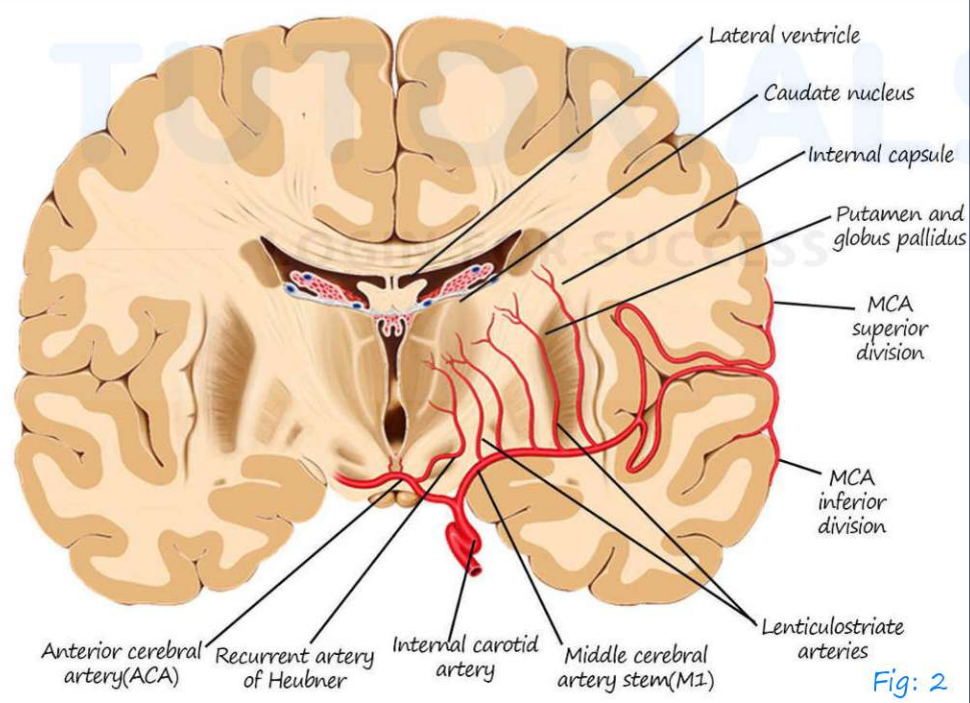

Fig: 2

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- 3mm – 2cm infarcts
- Pathology: Either lipohyalonosis / atherothrombosis
- Also referred to as lacunar stroke

↓

Lacunes / lakes

(Small size infarcts)

- Clinical presentation: pure motor stroke

  Pure sensory stroke (Thalamus)

  Ataxic hemiparesis (ventral pons)

  Dysarthria clumsy hand syndrome
- Principle risk factors: HTN, Age

Cardioembolic stroke 00:16:40

- Source: Atrium

  Valve

  Ventricle

  Aorta

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TOAST Classification of High and medium risk sources of classification

- High risk sources
  - Mechanical prosthetic valve
  - Mitral stenosis with atrial fibrillation
  - Atrial fibrillation (other than lone atrial fibrillation)
  - Left atrial/atrial appendage thrombus

- Sick sinus syndrome
- Recent myocardial infarction (<4 weeks)
- Left ventricular thrombus
- Dilated cardiomyopathy
- Akinetic left ventricular segment
- Atrial myxoma
- Infective endocarditis

- Most common cause cardioembolic stroke – non rheumatic atrial fibrillation
- Medium risk sources
  - Mitral valve prolapses
  - Mitral annulus calcification
  - Mitral stenosis without atrial fibrillation
  - Left atrial turbulence (smoke)
  - Atrial septal aneurysm
  - Patent foramen ovale
  - Atrial flutter
  - Lone atrial fibrillation
  - Bioprosthetic cardiac valve
  - Nonbacterial thrombotic endocarditis
  - Congestive heart failure
  - Hypokinetic left ventricular segment
  - Myocardial infarction (>4 weeks, <6 months)
  - Cardioembolic stroke → large strokes
    → multiple vascular territories involved
    → maximum defect at onset

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→ seizures at onset

→ poor prognosis

Stroke of other determined etiology 00:25:18

- Arterial dissection
- Vasculitis

Stroke of other undetermined etiology 00:25:50

- Even after extensive evaluation, cause could not be found

(or)

- Evaluation is incomplete
- 2 or more possible cause

Most common stroke subtype – large artery disease.

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GENETIC CAUSES OF STROKE

Causes 00:00:20

- Single gene disorders – cadasil
- Multisystem disease – sickle cell anemia
- Genetic polymorphism

Genetic disorders associated with stroke

- CADASIL
- Carasil
- Fabry's disease
- RVCL
- Col_4 A_1 gene related SVD

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Others

- Sickle cell disease
- Marfan's syndrome
- Ehler Danlos syndrome
- Pseudoxanthoma elasticum
- Melas (Mitochondrial encephalopathy lactic acidosis stroke like episodes)

Cadasil 00:04:00

- AD
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

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- Age: – 4th / 5th decade
- Clinical features
  - Young stroke
  - Small vessel disease
  - 40% can have migraine with arua
  - Dementia
  - Depression
  - Cognitive disturbances

Cadasil encephalopathy / Cadasil coma → patient is almost in coma

- Cause: – NOTCH 3 gene mutations [Q]
- Imaging: –
  - T2 Flair Axial Sequence

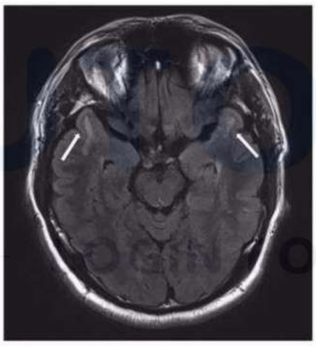

Fig: 1

Early feature: – temporal pole symmetric hyperintensity

↓

O' Sullivan sign

– More diffuse white matter changes

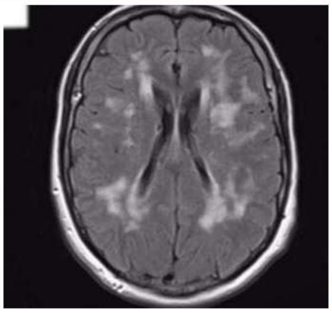

Fig: 2

T2 Axial flair → Extensive white matter changes that occur symmetrically

- Diagnose: -

  Notch 3 gene mutation

  Skin biopsy

  ↓

  Granular osmiophilic deposits (GOM) in tunica media

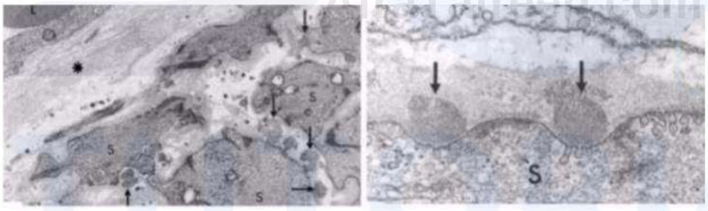

Fig: 3

- Treatment: - no specific treatment
- Most common cause of inherited genetic stroke

Carasil 00:11:54

- Autosomal recessive
- $HTRA_1$ gene mutation
- Age: - 3rd decade of life
- Presentation similar to that of cadasil except migraine

  ↓

  Alopecia +

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Low back pain (Disc bulging)

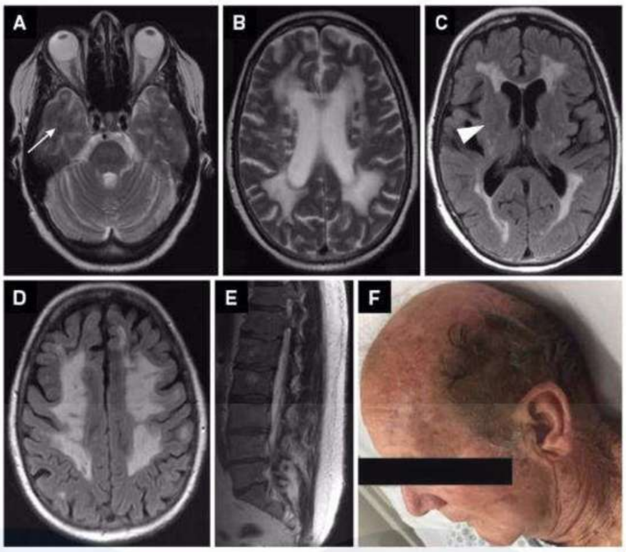

Fig: 4

- Treatment: - no specific treatment

Fabry's disease 00:14:28

- X – linked
- Lysosomal storage disorder
- GAL gene → α galactosidase A
- Clinical: -
  - 3rd decade of life
  - Young stroke
  - Hearing loss
  - Posterior circulation stroke
  - Posterior circulation dolichoectasia

    ↓

    Elongated and dilated
  - Cornea verticillate/vertex keratopathy

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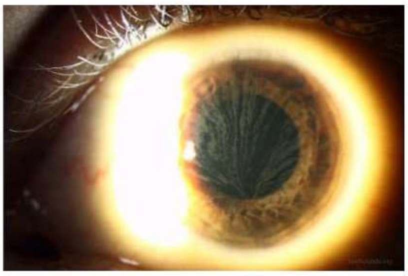
Fig: 5

↓

Whorl like deposits

Produced by amiodarone

- Angiokeratomas → swimming suit distribution

Fig: 6

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- Painfull acroparathesias – feature of fabry's
- Imaging - T1 axial sequence

↓

Hyperintensity in lentiform and pulvinar nucleus

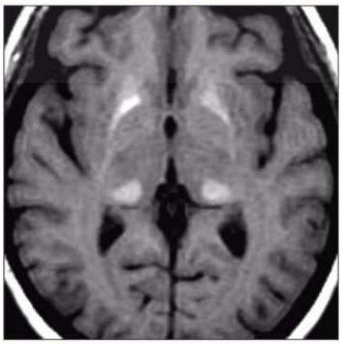
Fig: 7

- Dilated basilar artery

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Fig: 8

- Treatment: - enzyme replacement therapy
- Diagnosis: - α – galactosidase A leukocytes and plasma
- **RVCL** – Retinal Vasculopathy with Cerebral Leukodystrophy.
- COL4 A1 gene related small vessel

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YOUNG STROKE

- Stroke in < 45 years old individual
- Most common etiology in these – atherosclerosis

Etiology 00:02:28

1.Cardiac causes

- Patent foramen ovale
- Mitral stenosis
- Atrial fibrillation
- Atrial septal aneurysm

2.Pro-coagulant states

- Virchow's triad
- Obesity
- Post-partum
- OCP's → venous stroke
- Factor V Leiden mutation
- Protein C deficiency
- Protein S deficiency
- Antithrombin III deficiency
- Hyperhomocystinemia

3.Drugs

- Cocaine
- Amphetamine

4.Connective tissue diseases

- SLE

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- Sjogren's
- Sarcoidosis

5.Vasculitis

- Churg strauss syndrome
- Wegener's granulomatosis
- Polyarteritis nodosa
- Cryoglobinemic vasculitis

6.Vasculopathy

- Arterial dissection
- Moya moya disease
- AV aneurysm
- Berry aneurysm → SAH

7.Infections

- Infectious vasculitis
- TB meningitis
- Lyme disease
- Syphilis
- HIV

8.Traditional risk factors

- DM
- HTN
- Dyslipidemia

Conventional vascular risk factors	Chagas disease
	Trypanosoma cruzi
Age	Hepatitis C
Smoking	Infectious endocarditis

Dyslipidemia	Hematological diseases
Hypertension	Paroxysmal nocturnal
Diabetes	hemoglobinuria
Migraine	Thrombotic
synergistic effect of	thrombocytopenic purpura
smoking and OCP	Erythrocytosis
Pregnancy	Leukemias
Eclampsia	Intravascular lymphoma
Puerperium	Sickle cell disease, strongest
Oral comraceptive pills	associate
(with estrogen contest)	Cardiac conditions
Drug abuse (cocaine,	Patent foramen ovale
amphetamines)	Atrial septal aneurysm
	Atrial fibrillation -0.1% in
Specific diseases	young adults
Spontaneous arterial	Genetic determinants
dissection (hypertension	Cerebral autosomal
and genetic factor)	dominant/recessive
Fibromuscular dysplasia	arteriopathy with
of carotid and vertebral	subcortical
arteries	Infarcts and
Connective tissue	leukoencephalopathy
disorders	mutation in NOTCH 3 gene
Churg-Strauss	-HTRA
syndrome	1 gene
Polyamines nodosa	Fabry's disease
Behçet's disease	

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Inflammatory bowel disease Sarcoidosis SLE infectious diseases Lyme neuroborreliosis Tubercular meningitis Acute bacterial meningitis AIDS	Moya moya disease (6%-15% of non-atherosclerotic vasculopathy) Unconventional risk factors Sedentary lifestyle Drug abuse Oral contraceptives Alcohol Chronic infection (Chlamydia pre and periodontal disease) Raised apoB/apoA 1 ratio Obesity Physical inactivity Psychosocial stress Low fat and vegetable make OCP oral contraceptive pills SLE: system lupus erythematosus

	Test or procedure
Antiphospholipid syndrome	Lupus anticoagulant, anticardiolipin, and anti-B-2 glycoprotein antibodies

Systemic lupus erythematosus, other connective tissue diseases, Wegener's granulomatosis, Churg Strauss syndrome	ANA anti-ds-DNA, ENAS, complement, ANCA
Specific infections	Serum titres for syphilis, borrelia, zoster virus, hepatitis B and C virus, and HIV infection
Hepatitis C virus, other cryoglobulinemia's	Cryoglobulins
Illicit drugs	Serum and urine toxicological screening
Primary CNS and other vasculitis, CNS and systemic infections	CSF examination
Hyperhomocysteinaemia	Homocysteine concentrations
Specific deficiencies	Antithrombin III, protein S or C concentrations
Specific mutations	Factor V Leiden, prothrombin G20210A mutations

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Sickle-cell disease	Hemoglobin electrophoresis
Several inflammatory, infectious and genetic diseases, retinocerebral arteriopathies	Ophthalmological examination
Primary CNS and other medium and large-vessel vasculitis, non-atherosclerotic arteriopathies	Intra-arterial cerebral angiography
Periarteritis nodosa	Abdominal and renal angiography
Takayasu's disease	Aortic PET
Primary CNS vasculitis	Cerebromeningeal biopsy
Fabry's disease	GLA activity
CADASIL	Skin biopsy
MELAS	Muscle biopsy
Specific genetic diseases (Fabry's, CADASIL, HANAC syndrome, MELAS, etc.)	Genetic tests

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Moya moya disease 00:16:16

- Term moya moya comes from Japanese word meaning "Puff of smoke" appearance
- Vasculopathy
- Non atherosclerotic and non-inflammatory vasculopathy
- More common in Japanese population
- Occlusive disease

  Involves distal ICA and proximal ACA, MCA

  ↓

  Formation of collaterals

  ↓

  On angio-gives puff of smoke appearance

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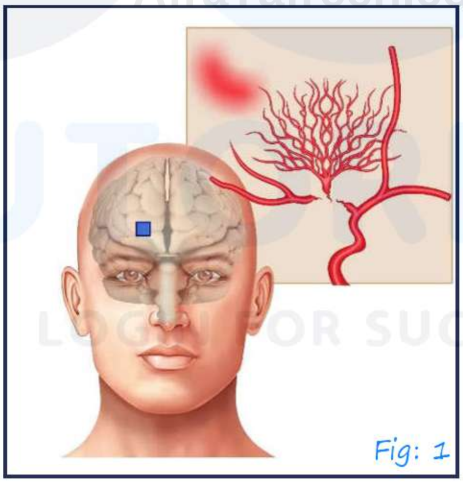

Fig: 1

- As the disease progresses, there occurs a ECA – ICA conversion → collaterals disappear
- Usually B/L
- Histological changes: -
  - Intimal hyperplasia
  - Disruption of internal elastic lamina

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- Proliferation of smooth muscle cells

- Clinical presentation: -
  - TIA
  - Ischemic stroke → children
  - Hemorrhagic stroke → adults
- Moya moya syndrome: -
  - Moya moya disease that occurs 2° to
- Atherosclerosis
- Radiation
- Thyroid disease
- Sickle cell disease
- Investigations
  - MRI Brain + MRA
  - DSA - Puff of smoke

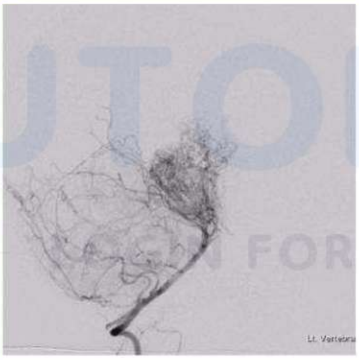

Fig: 2

  - HR VWI – high resolution vessel wall imaging
- Treatment
  - Antiplatelet prophylaxis
  - ICA – ECA bypass

Arterial dissection 00:26:46

- Blood vessel wall consists of tunica intima
  Tunica media
  Tunica adventitia
- Dissection: - Break in tunica intima
- Age: - 4th – 6th decade
- M = F (M > F)
- 2 types
  - Sub intimal dissection
  - Sub adventitial dissection

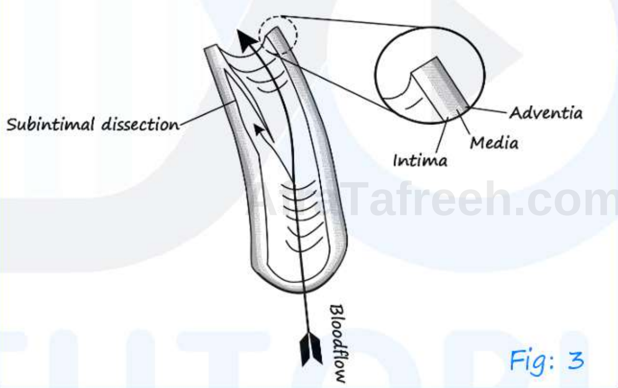

Fig: 3

- False lumen is created in sub intimal dissection

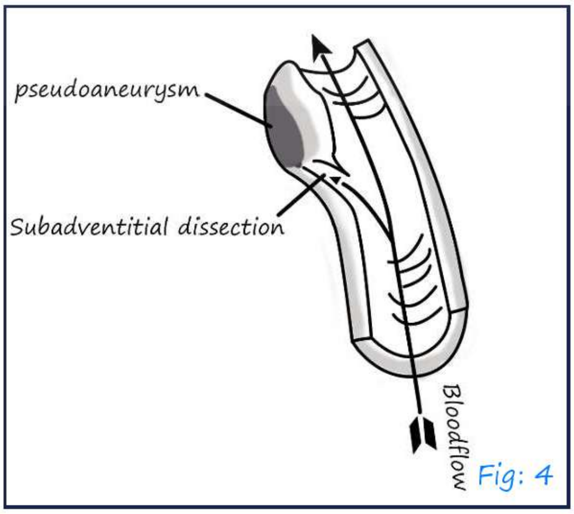

Fig: 4

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- Blood accumulates in the adventitial layer and forms pseudoaneurysm

- Predisposing factors
  - Marfan's syndrome
  - Ehler danlos syndrome
  - Osteogenesis imperfecta
  - Fibromuscular dysplasia
  - Trauma

- Dissection can involve → extracranial circulation
  → intracranial circulation
  ↓
  Carotid circulation (or) vertebrobasilar circulation
- Intracranial dissection → more chances of bleed
  ↓
  SAH
- Extracranial dissection
- V_2, V_4 Segments of vertebral artery more prone for dissection
- Clinical features
  - Headache
  - Neck pain
  - Visual symptoms
  - Horner's syndrome
  - Cranial verve palsies

TUTORIALS
LOGIN FOR SUCCESS

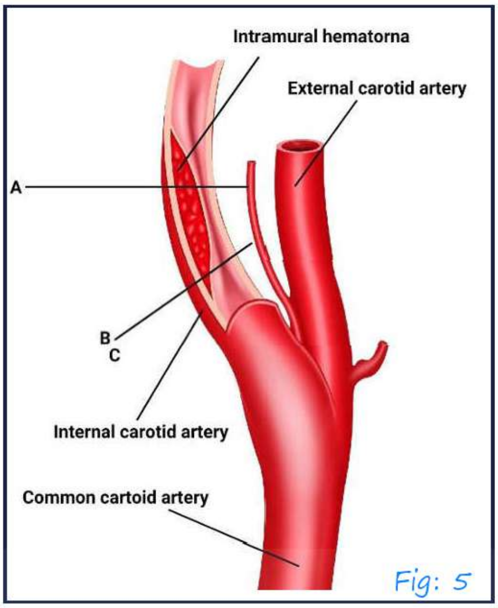

Fig: 5

- Investigations
  - CT Angiogram
  - MR Angiogram
  - Doppler – neck vessel doppler
  - DSA- Digital Subtraction angiography (Gold standard)
  - HR VMI

Fig: 6

Crescent sign: - hypo intensity surrounded by eccentric Hyperintensity

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- Treatment
  - Acute ischemic stroke
- Extracranial dissection → Thrombolyse
- Intracranial dissection → Thrombolyse
  - Prophylaxis

    2015 → CADISS trial

    ↓↓

    Antiplatelet = Anticoagulation
  - Angioplasty ± stenting

Fibromuscular dysplasia 00:42:24

- F>M
- Age: - 50 years
- Hyperplastic disorder of vessel wall
- Areas of stenosis with intervening, Normal or dilated areas create a String of beads appearance on angiography
- Can affect your cervical arteries – carotid and vertebral arteries
  - Renal arteries
  - Iliac and subclavian arteries
- Clinical features:
  - TIA
  - Stroke
  - Increased predisposition for carotid dissection

    String of beads appearance

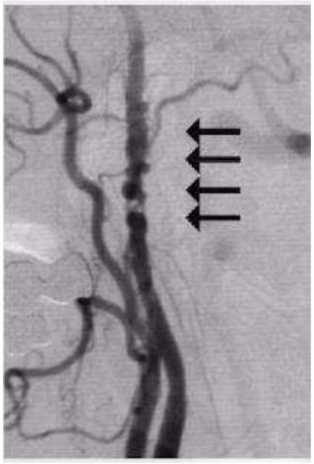
Fig: 7

- Treatment: – Initial: – Thrombolysis

  Long term: – Antiplatelets/Anticoagulants

Vasculitis 00:47:20

- 1° vasculitis affecting CNS: – Example: – Wegener's
- 2° vasculitis affecting CNS: – example: – SLE
- PACNS: – Primary angiitis of CNS (or) primary CNS vasculitis
  - Rare disorder
  - Males
  - Angiitis limited to brain, meninges and spinal cord
  - Clinical features: –
- Headache
- Cognitive disturbances
- TIA
- stroke
  - Investigations: – Diagnosis of exclusion
- MRI Brain with contrast
- DSA – gold standard → areas of stenosis

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- Brain biopsy/meningeal biopsy
  - Transmural inflammation
  - Fibrinoid necrosis
- CSF study → increase cells, increase protein
  - Treatment – D.O.C
- 6 months – 1 year.

TUTORIALS
LOGIN FOR SUCCESS

BASICS PRINCIPLES OF STROKE LOCALIZATON

Basic principle of stoke localization 00:00:30

- Motor
- Sensory
- Speech
- Cranial nerves
- Balder
- Cerebellum and its connection

Hemiplegia

- Lesion above C5 level → cord

Brainstem

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Internal capsule

Corona radiata

Cortex

TUTORIALS LOGIN FOR SUCCESS

Motor domain 00:06:20

- Motor pathway – descending pathway
- Origin: - pyramidal cells of motor cortex – UMN (Betz cells)
- Referred to as pyramidal pathway / cortisol spinal tract

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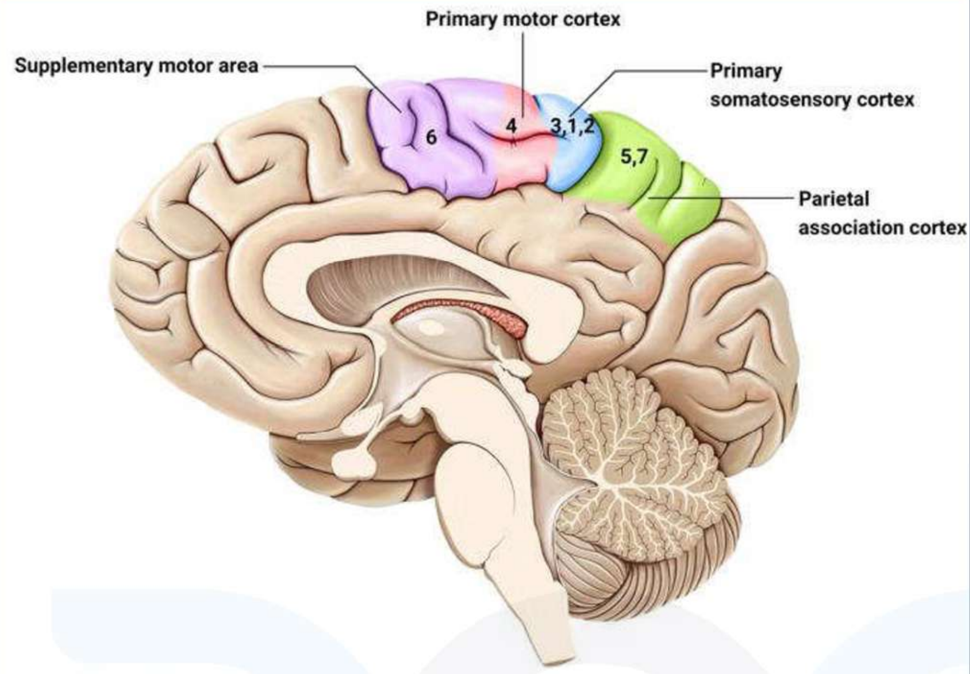

lateral view of cerebellum Fig: 1

- Premotor cortex
- Supplementary motor area — origin of pyramidal pathway
- Primary motor area
- Central sulcus
- Representation of motor homunculus and sensory homunculus is in inverted manner
- Hand and face (area of fine movement s) have large representation
- Motor pathway originates from motor cortex and descends down passes through internal capsule enters mid brain (and part), pons and further descends to upper part of medulla and pyramidal decussation occurs in owe part of medulla → 80% pf fibers cross sand continue as lateral corticospinal

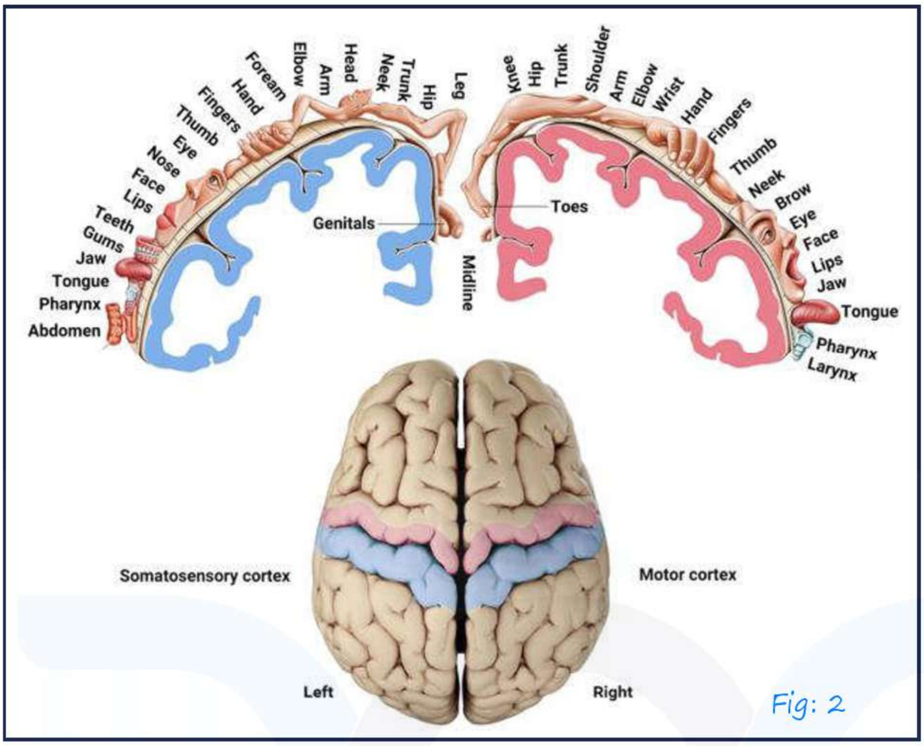

Fig: 2

- 20 % would not cross and that forms the anterior corticospinal tract
- α Motor neuron in spinal cord → supplies arm
- lateral corticospinal tract ends at anterior horn cells
- anterior corticospinal tract crosses just before termination

function of anti-corticospinal tract

- maintaining posture and equilibrium

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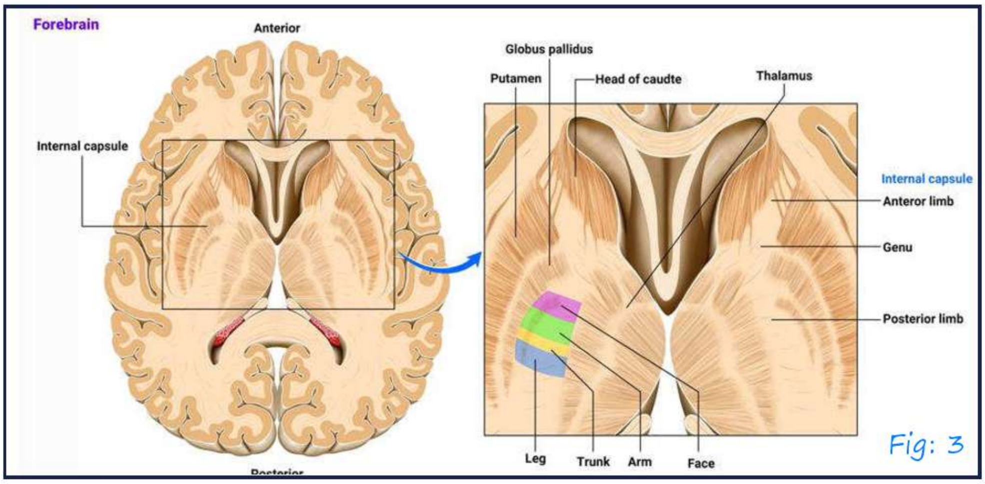


Fig: 3

- motor pathway is descending though Geenu and ant 2/3 of posterior limb

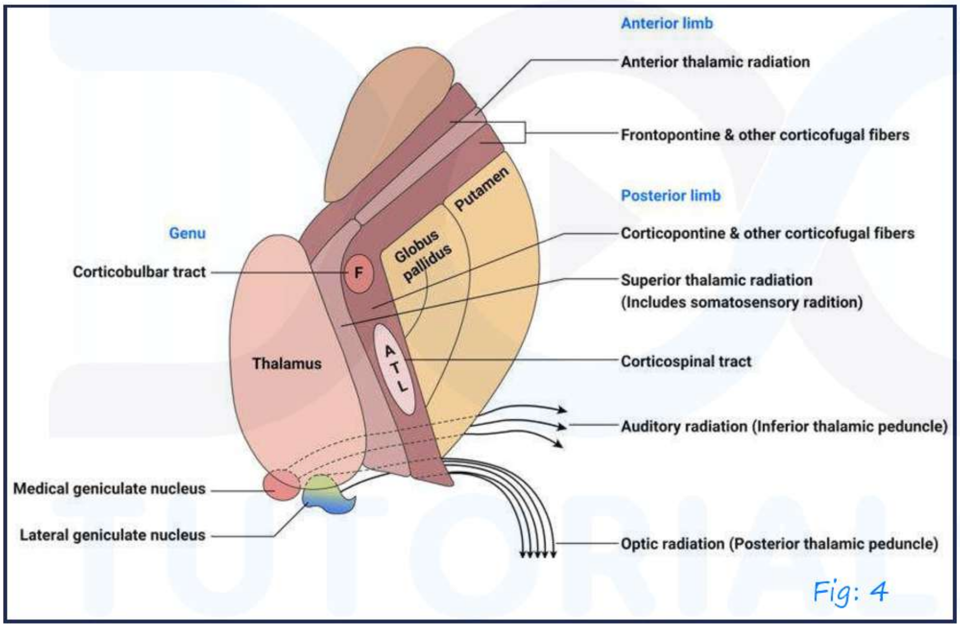
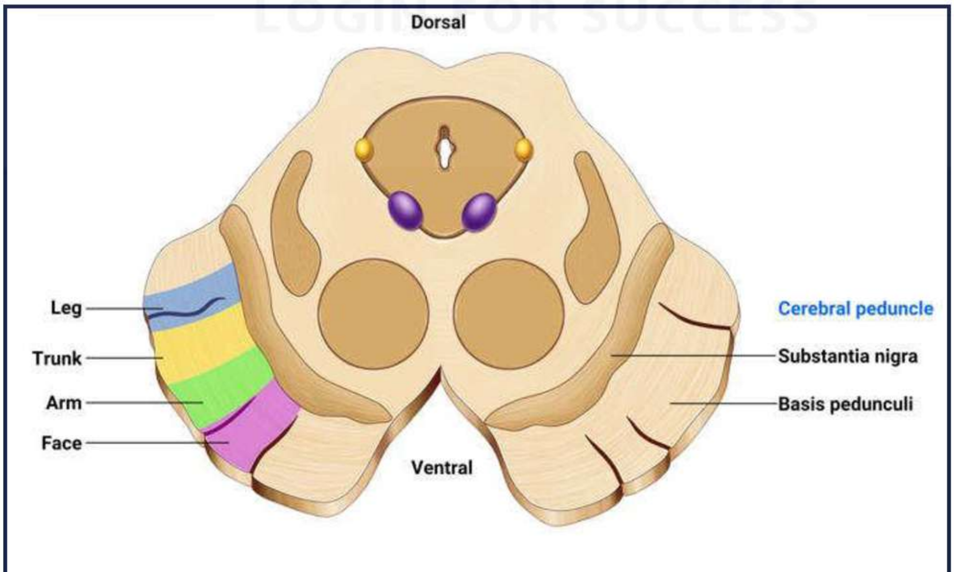


Fig: 4



b. Midbrain

Fig: 5

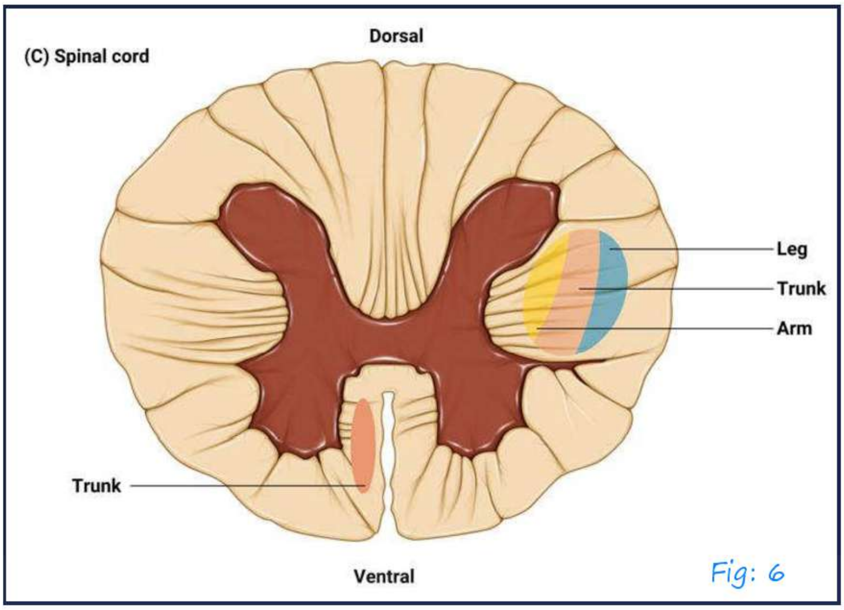


Fig: 6

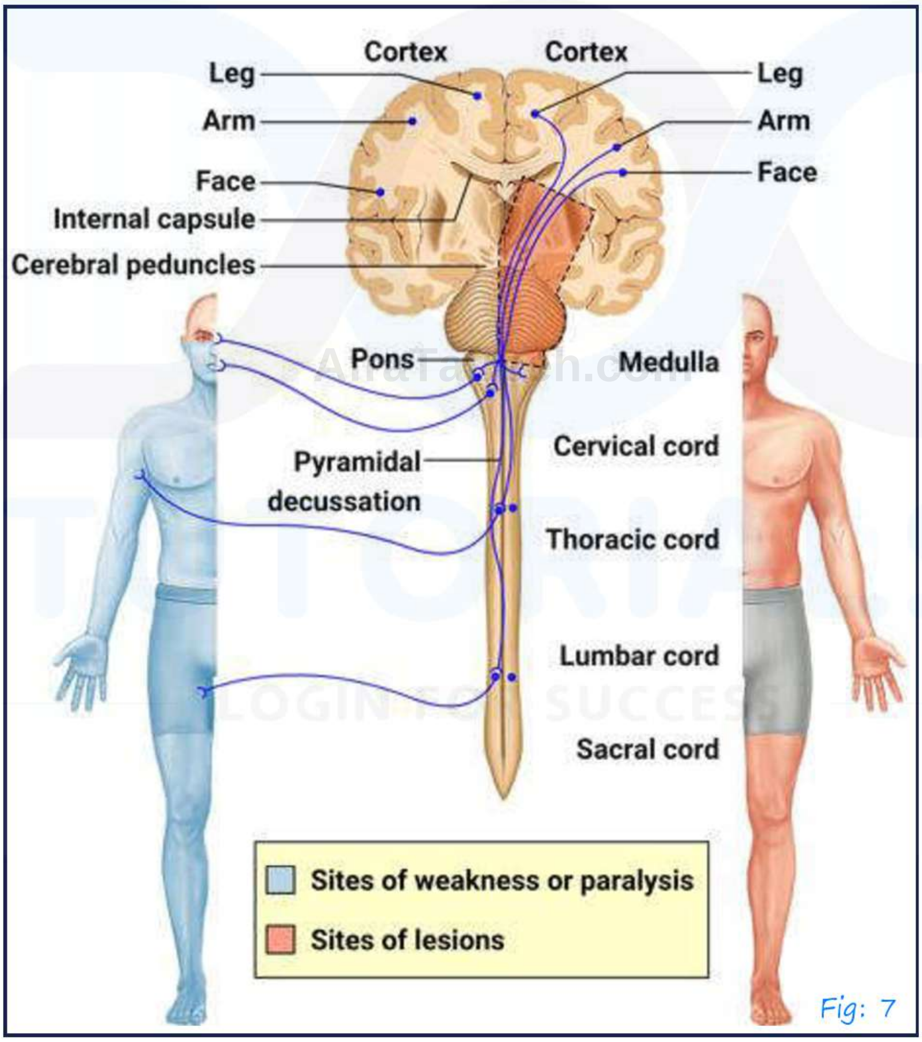


Fig: 7

→ coronal such on of brain

- lesion in internal capsule – Hemiplegia (C/l)

↓

Dense

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- dense hemiplegia → UL weakness equal to lower limb weakness
- upper part of face spared
- lesion in cortex and IC→ Dense hemiplegia
  → cortical features
  → increase ICT
- lesion in cortex only → Hemiplegia with sparing of weakness

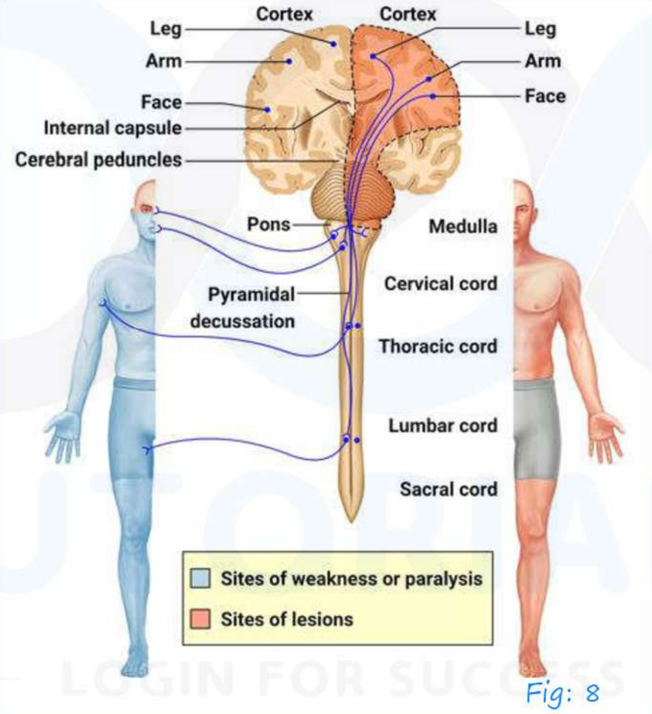

Fig: 8

- lesion in medulla and cervical cord → C/L hemiplegia sparing face
- lesion in cortex involving face and arm area

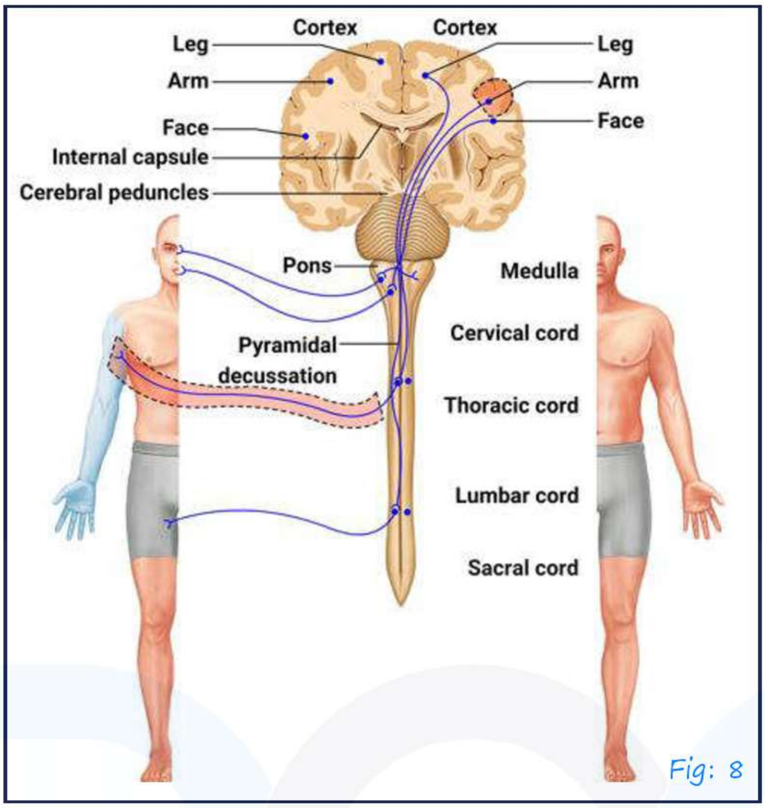

Fig: 8

C/L monopoiesis

- lesion involving only leg

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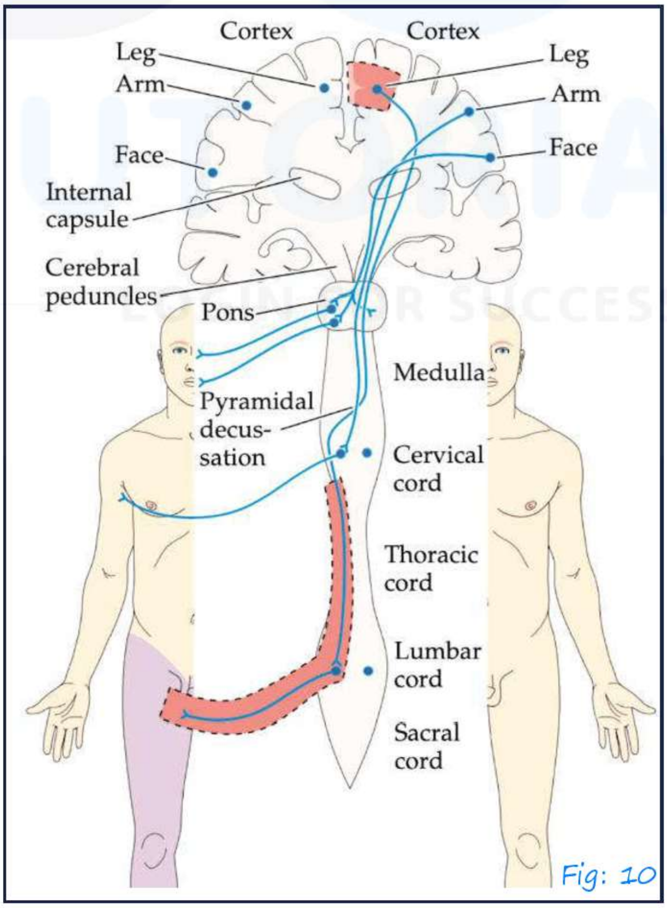

Fig: 10

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C/L crural monopoiesis

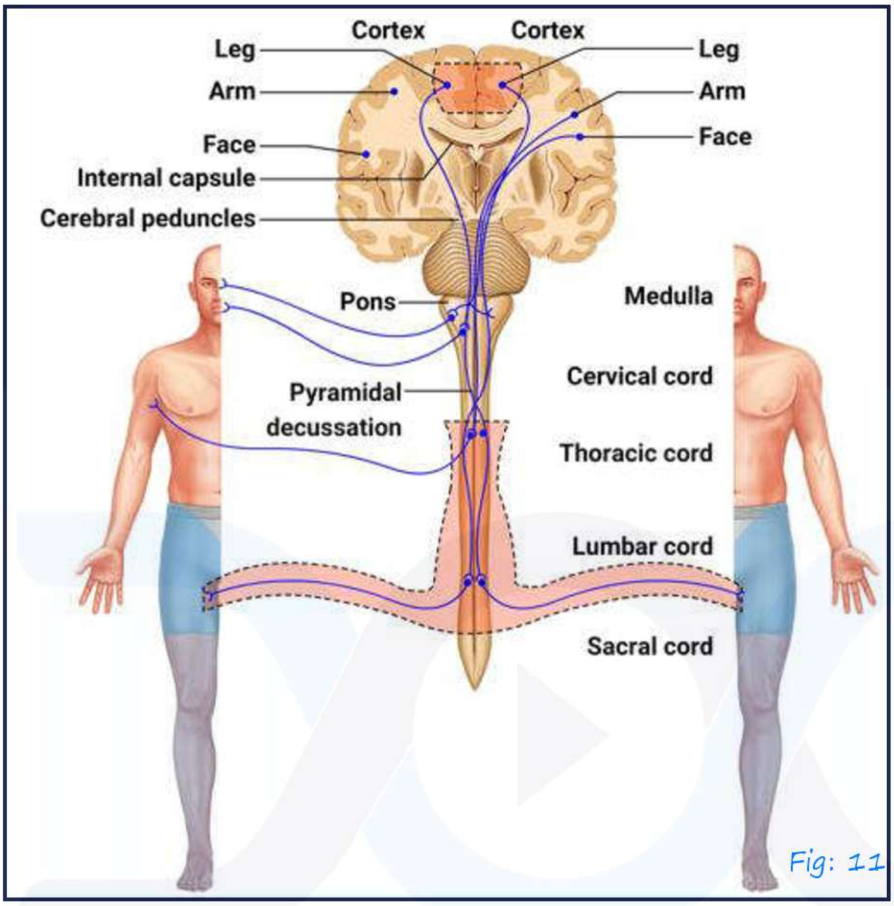

Fig: 11

- Simultaneous involvement of both leg area

↓

paraparesis

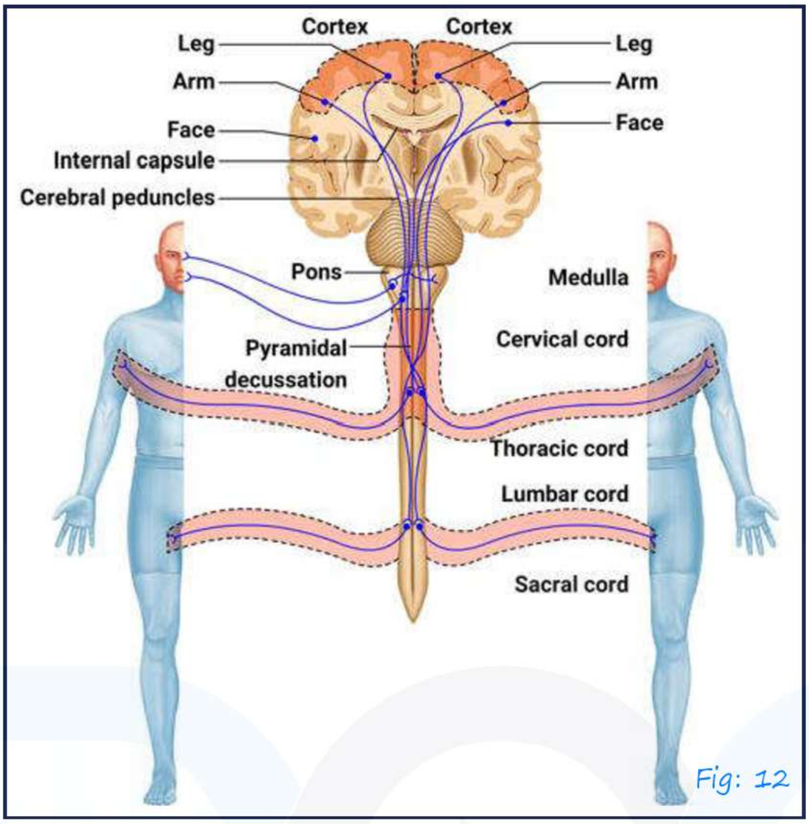

Fig: 12

↓

- lesion in B/L cortex – Quadriparesis

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Sensory Domain 00:42:48

- Sensory pathway are ascending pathways
  - Dorsal column pathway → carries light touch, joint vibration position sense, vibration
  - spinothalamic pathway
    - Ant – crude touch
    - lateral – pain, temperature

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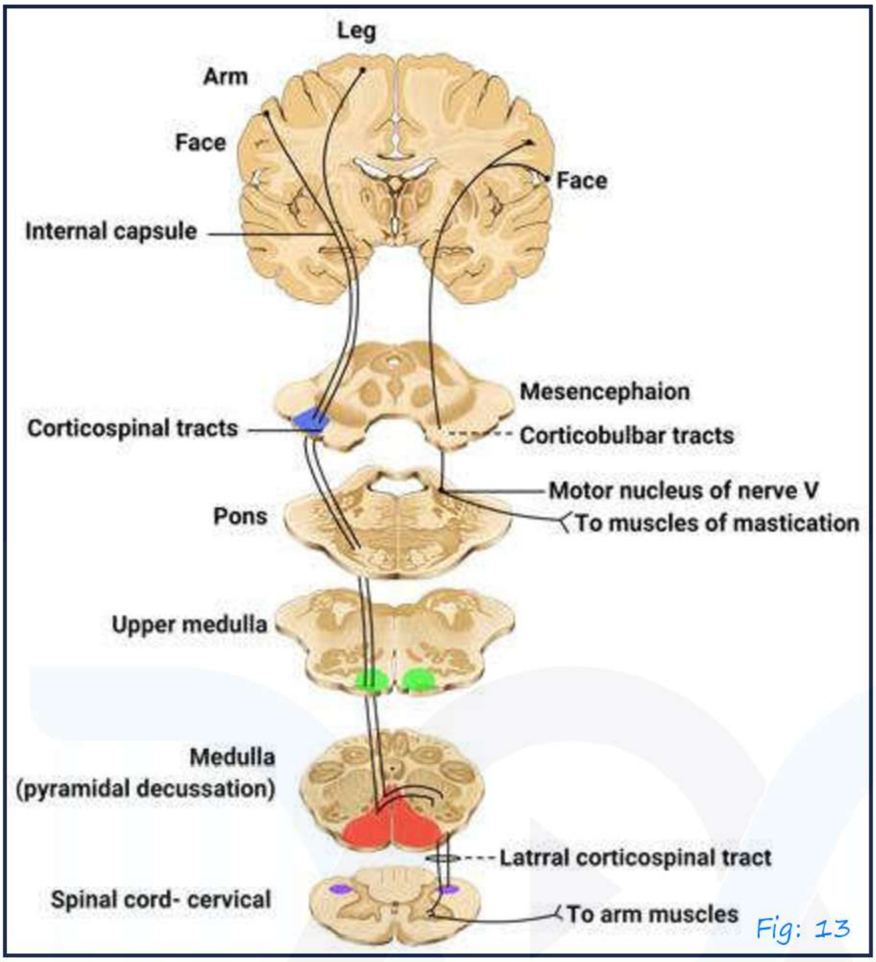

Fig: 13

- Dorsal column pathway
  - Arises from dorsal horn and without synapsing, its ascending
  - Ascends through, fasciculus gracile → fibers from LL

    Fasciculus cuneatus → fibers from UL
  - reaches medulla, synapses with nucleus of fasciculus gracilus andcuneatus
  - Second order neurons from medulla cross the opposite side and farther ascends u → medial lemniscus
  - Next synapse is at ventro posterolateral nucleus of thalamus

Spinothalamic tract

- Arises from dorsal horn, reaches spinal cord
- First order neurons synapse at substantia gelatinous
- Second order neurons arise, crosses and ascends as lateral spinothalamic tract
- Ascends up and synapses at ventral posterolateral nucleus of thalamus → thalamic radiation
- Facial nerve sensations are carried by trigeminal nerve

  ↓

  Separate pathway → Trigemini thalamic pathway

  (or) Quinto thalamic pathway

  Synapse at ventro posteromedial part of

  Thalamus

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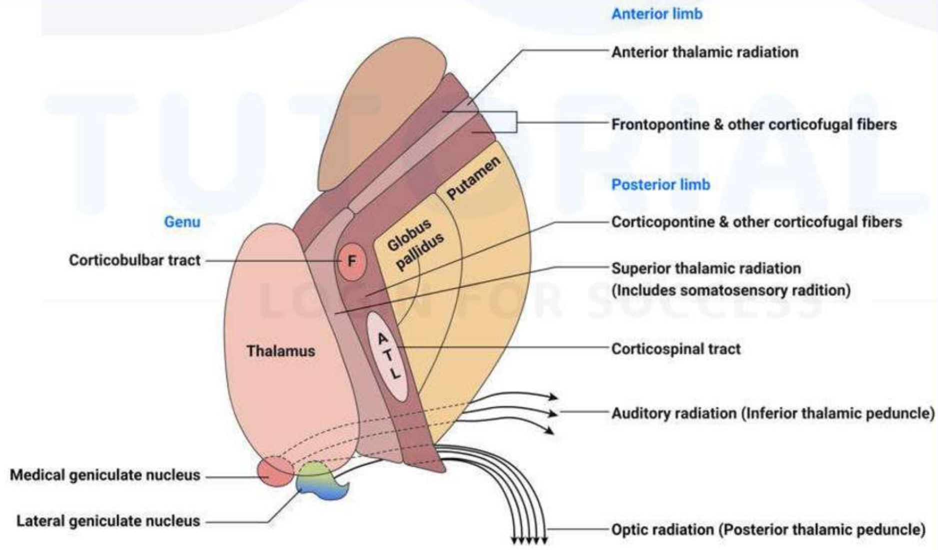

Fig: 14

- Cortical sensations require intact cortex for appreciation
- Cortical sensation → tactile localization

  Two-point discrimination

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Graphesthesia

Stereognosis

Double simultaneous stimulations

- Superficial sensations – pain
  -temp ⊢ lost in thalamic lesion
- Deep sensation – vibration

Joint position sense

Sense of passive movement

- for appreciating cortical sensation

↓

1° modality of sensation should be intact

- Any lesion above thalamus

↓

Only cortical sensation affected

Cranial nerves 00:56:16

- 12 pairs of CN
- 10 pairs – brainstem
- Most of the cranial nerves arise from ventral aspect, except tracheal never – dorsal aspect

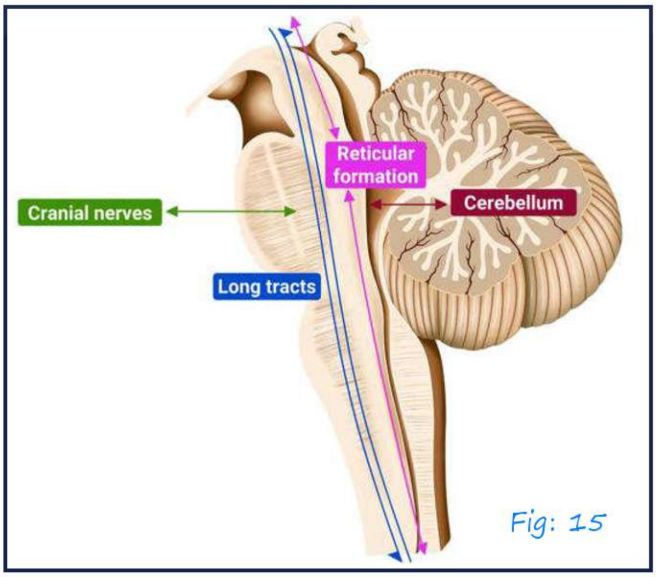

Fig: 15

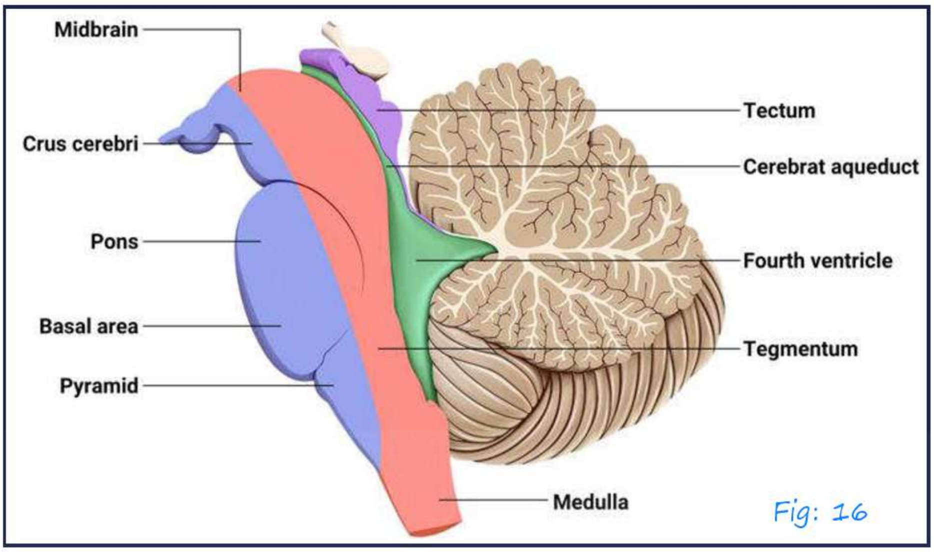

Fig: 16

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- Rule of 4: - 4 structures medially – M
  - Motor pathway
  - Medial meniscus
  - Medial longitudinal fasciculus
  - Motor cranial nuclei
- Structures laterally – S
  - Spinothalamic pathway
  - Spinocerebellar pathway
  - Spinal nucleus & tract of v th nerve
  - Sympathetic
- Motor cranial nerve nuclei are divisible by 12
- 4 cranial nerves emerge above pons
  - Cranial nerves emerge in pons (5,6,7,8)
  - Cranial nerve emerges in below pons (9,10,11,12)
- Crania-caudal localization – cranial nerve affection helps in localization

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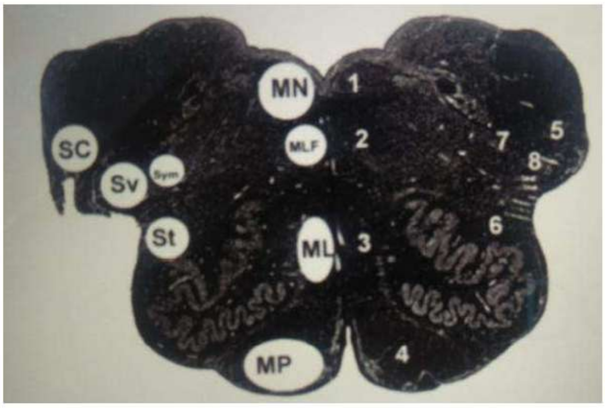

Fig: 17

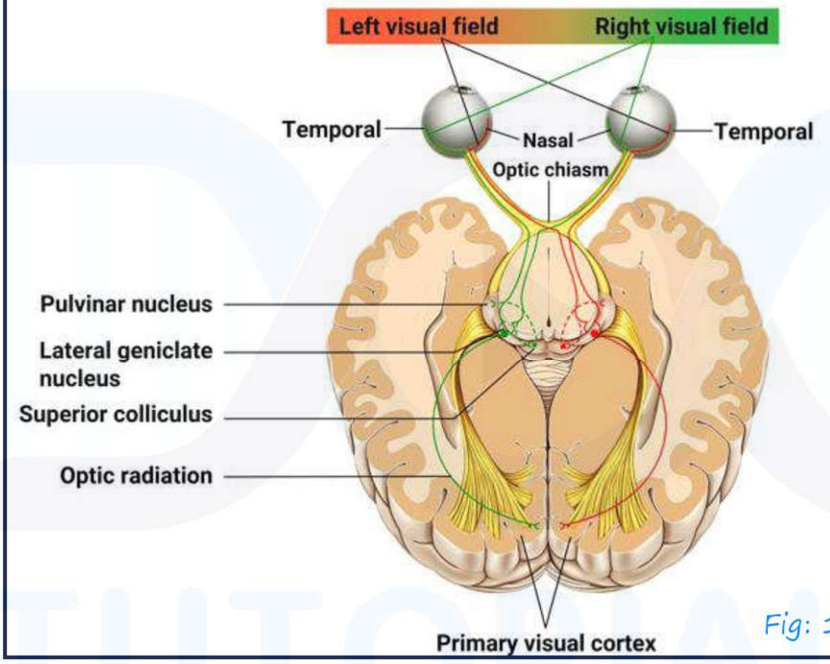

Fig: 18

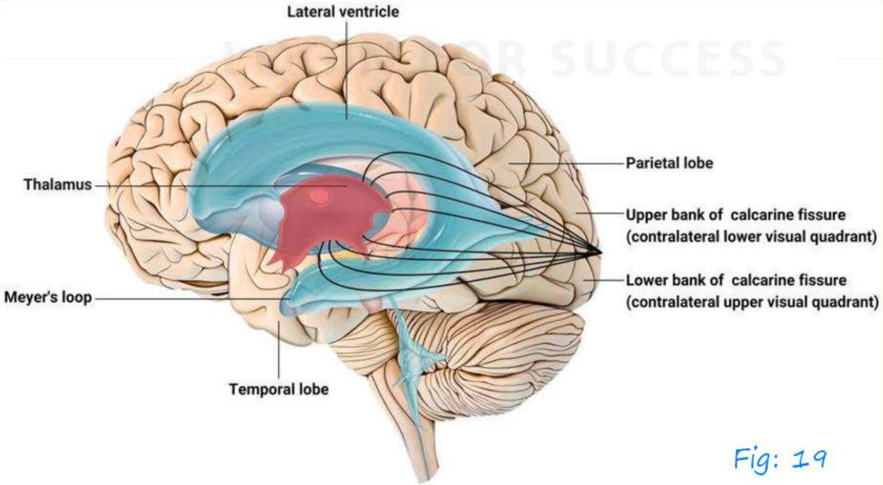

Fig: 19

- Superior part of optic radiation goes through the parental lobe

- Interior optic radiation – temporal lobe → forms mayor's 100 P
- Optic radiation in relation to internal capsule
- Lesion in internal capsule

  C/L hemiplegia

  Hemianesthesia

  Homonymous hemianopia

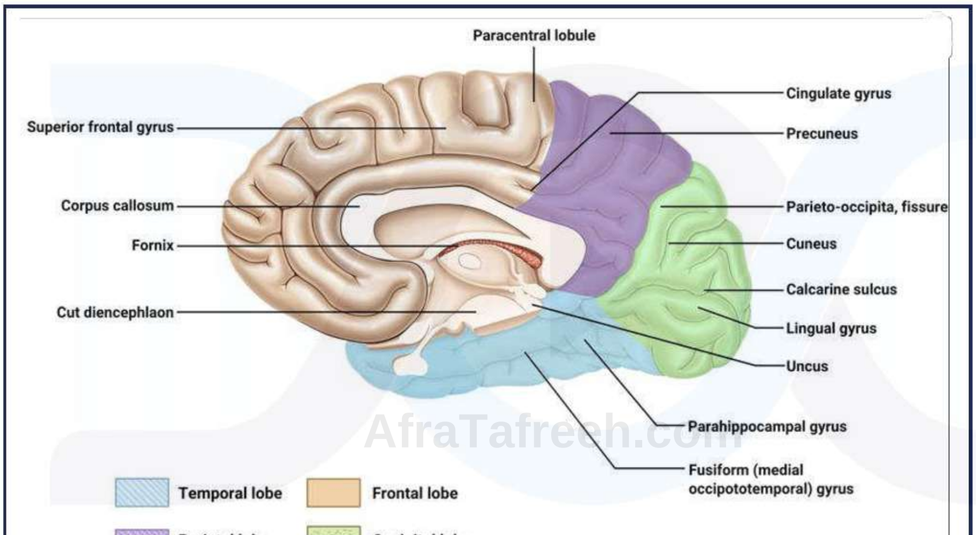

Fig: 20

- Calcaneal sulcus divides occipital lone into cuneus & lingual gyrus
- Area just above and below calcaneal sulcus is 1o visual area (area 17)
- Other than 1o visual area → visual association area (18,19)
- Upper ½ of calcaneal sulcus receives fibers from upper part of retina and lower ½ from lower part of retina
- Lowe retinal fibers – upper visual filed
- Upper retinal fibers – lower visual field

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Lesion of occipital lobe

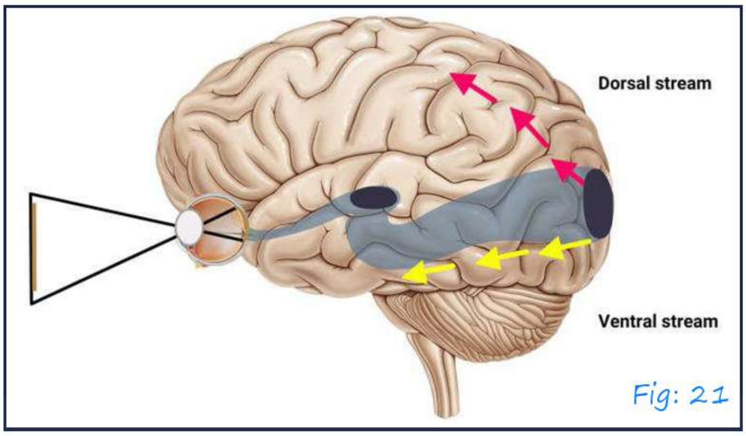


Fig: 21

- Ventral stream pathway – what pathway
  - From occipital lobe → interior temporal lobe
  - Important from recognition of objects faces, words & colors
- Dorsal stream – were pathway

  ↓

  - From occipital lobe → superior parietal cortex
  - Important for visuospatial recognition

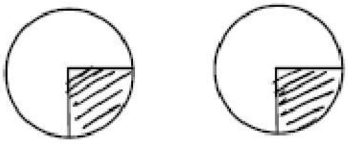
Lesion of 1° visual cortex

- Visual field defects

  Left occipital lobe lesion

Right homonymous hemianopia

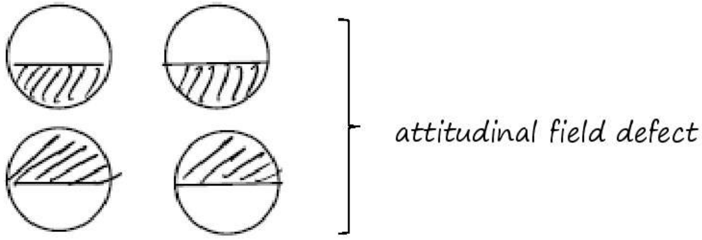
Left occipital – upper part of calcarine sulcus



Right homonymous lower quadrantopia

Light occipital – lower part of calcarine sulcus

- Pupillary reaction is spared



- 1 o visual cortex is having blood supply from posterior cerebral artery (calcarine branches)
- Representation of mocular vision is at occipital pole

→ blood supply by PCA+ MC branch

↓

Mocular sparing

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Cortical blindness

- Vascular insult to posterior circulation – B/L striate cortex

↓

Cortical blindness

(Macula sparing pupillary

Reflexes spared)

- B/ L affection of 1o visual cortex + visual association area

↓

- Cortical blindness
- Denial of blindness (visual anosognosia)

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Lesion of ventral stream

- Visual object agnosia
- Color vision abnormalities
- Prosopagnosia

↓

- Difficulty in identity familiar faces
- B/L ventral stream defect
- B/L occipitotemporal gyrus (fusiform gyrus)

Lesion of dorsal stream

- Balint's syndrome

Sensation of face 00:03:00

- Trigeminothalamic tract/ Quintothalamic tract

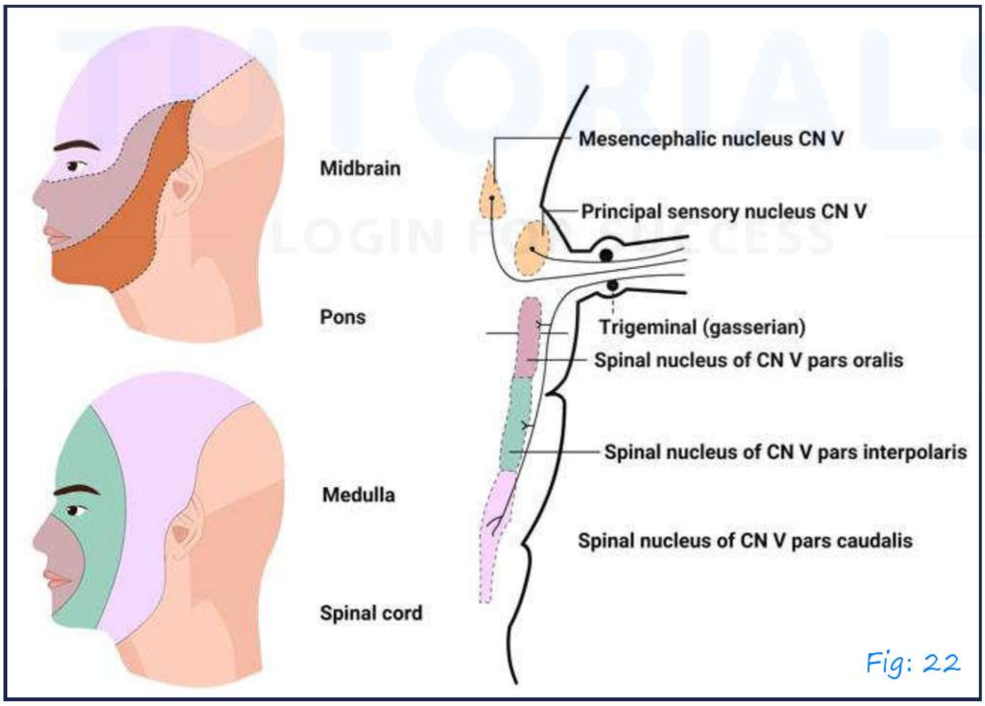
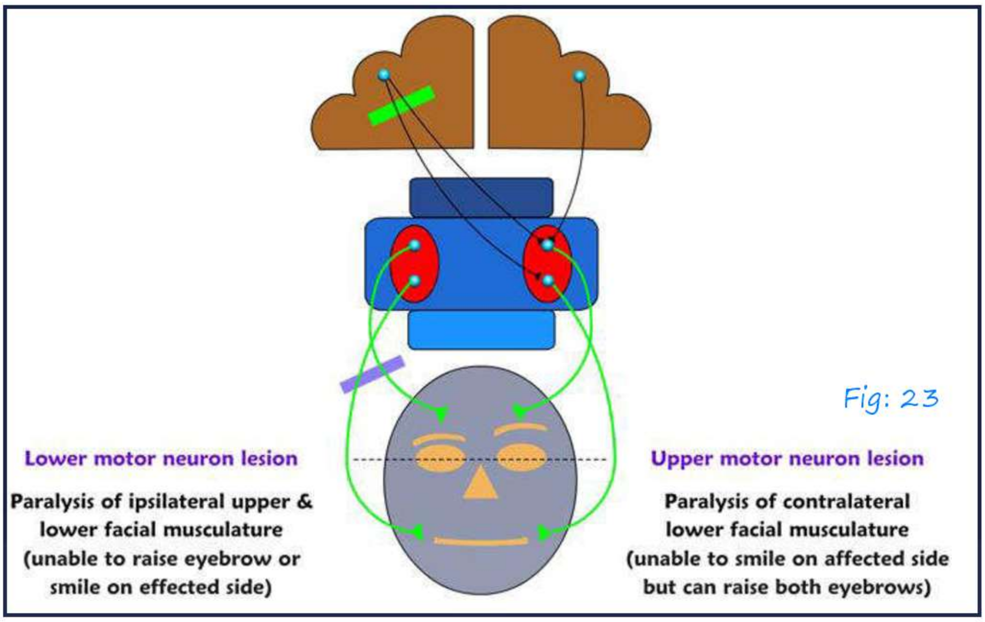


Fig: 22

- Onion peel pattern of sensory distribution + specific pathology



- Upper part of facial nucleus receives fibers from both contexts
- Corticobulbar fibers → UMN
- All CN have bilateral supply except 7th nucleus lower part
- Right corticobulbar affection – Left UMN facial palsy
- Crossed hemiplegia – cranial nerve involvement on one side and weakness on other side

Speech and language 00:49:49

- Language: - sounds, symbols, gesture
- Speech" – phonetic aspects of verbal expression

Wernicke Gershwin model

- 7 areas

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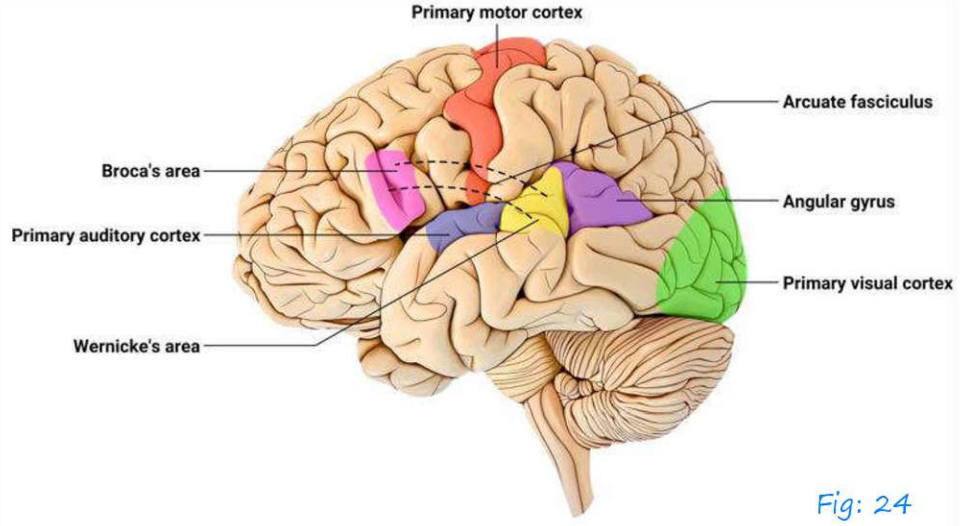

Fig: 24

- Angular gyrus – area 39
  - naming and world finding
- Wernicke's area – area 22
  - posterior part of superior temporal gyrus
  - comprehension of written and spoken language
- Broca's area – area 44
  - post part of interior of frontal gyrus
  - fluent output & grammer
- Arcuate fasciculus – connects Broca's and Wernicke's area

Aphasia

- Disturbance in central speech apparatus
- Defined as defect in production/comprehension written or spoken acquired lesion in brain

Dysarthria

- Defect in peripheral speech apparatus
- Defect in articulation of speech
- Language represented in dominant hemispheres
- Speech and praxis are located in dominant hemisphere
- Core of language network – perisylvian language network

BOSTON classification

I. Broca's aphasia
II. Wernicke's aphasia
III. Global aphasia
IV. Anomic aphasia
V. Conduction aphasia
VI. Transcortical sensory aphasia
vii. Transcortical motor aphasia
viii. Transcortical mixed aphasia (Isolation aphasia)

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Bedside language examination

- Spontaneous speech
  - Informal interview
  - Structured task
  - Automatic
- Naming
- Auditory comprehension
- Repetition

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- Reading
  - Reading aloud
  - Reading comprehension
- Writing
  - Spontaneous sentences
  - Writing to dictation

Broca's aphasia

- Decreased word output (non-fluent aphasia, motor aphasia)
- Agrammatism
- Phrase length -diminished (Telegraphic speech)
- Comprehension – preserved
- Repetition – affected

Beside Features of Broca Aphasia

Features	Syndrome
Spontaneous Speech	Non fluent, mute, or telegraphic, usually dysarthric
Naming	Impaired
Comprehension	Intact (mild difficulty with complex grammatical phrases)
Repetition	Impaired
Reading	Often impaired ("third alexia")
Writing	Impaired (dysmorphic, dysgrammatical)
Associated signs	Right hemiparesis Right hemisensory loss ± Apraxia of left limbs

Wernicke's aphasia

- Comprehension defect
- Fluent aphasia
- Paraphasia's → substituting in language
  - Phonemic paraphasia – "hen" repeated as "pen"
  - Neologism – completely new word with no meaning
  - Semantic – "pencil" repeated as "Pen"
- Jargon speech
- Impaired repetition

Beside Features of Wernicke's aphasia

Features	Syndrome
Spontaneous Speech	Fluent, with paraphasic errors usually not dysarthric sometimes logorrheic
Naming	Impaired (oftern bizarre paraphasic misnaming)
Comprehension	Impaired
Repetition	Impaired
Reading	Impaired for comprehension, reading aloud
Writing	Well-formed, paragraphic
Associated signs	± right hemianopia motor, Sensory signs usually absent

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Condition aphasia

- Lesion in dorsal perisylvian /Temporo-parietal region
- Paraphasia's'

Anomic aphasia

- Defect in angular gyrus
- Naming and world finding defect

Bedside Features of anomic aphasia

Features	Syndrome
Spontaneous Speech	Fluent, some word-finding pauses, circumlocution
Naming	Impaired
Comprehension	Intact
Repetition	Intact
Reading	Intact
Writing	Intact, except for anomia
Associated signs	Variable or none

- m/c aphasia syndrome in trauma, metabolic syndrome,

  Alzheimer's dieses

Transcortical aphasia

- Lesion disconnecting perisylvian language network from association area
- Result of watershed infarcts
- Divided into → transcortical motor → similar to Broca's aphasia
  - → Isolation aphasia
  - → transcortical sensory → similar to Wernicke's
  - ↘ Repetition preserved

Beside features of transcortical aphasias			
Feature	Isolation syndrome	Transcortical motor	Transcortical sensory
Speech	Non fluent echolalic	Nonfluent	Fluent, echolalic
Naming	Impaired	Impaired	Impaired
Comprehension impaired	Impaired	Intact	Impaired
Repetition	Intact	Intact	Intact
Reading	Impaired	+ intact	Impaired
Writing	Impaired	+ intact	Impaired

Pure alexia 9alexia without agraphia)

- Patient not able to read, but can write
- Lesion that disconnects visual input to language area
- Lesion: – left occipital cortex + splenium → Right homonymous hemianopia

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Bedside features of pure alexia without agraphia	
Feature	**Syndrome**
Spontaneous speech	Intact
Naming	+ impaired, especially colors
Comprehension	Intact
Repetition	Intact
Reading	Impaired (some sparing of single letters)
Writing	Intact
Association signs	Right hemianopia or superior Quadrantanopia Short-term memory loss Motor, sensory signs usually absent

Alexia with agraphia

- Lesion in angular gyrus
- Reading and writing impaired

Pure world deafness

- Disconnection of auditory associated areas from language network

Clinical Features of Aphasias and Related Conditions Commonly Seen in Cerebrovascular Accidents

	Comprehension	Repetition of spoken language	Naming	Fluency
Wernicke's	Impaired	Impaired	Impaired	Preserved or increased
Broca's	Preserved (except grammar)	Impaired	Impaired	Decreased
Global	Impaired	Impaired	Impaired	Decreased
Conduction	Preserved	Impaired	Impaired	Preserved
Nonfluent (anterior) transcortical	Preserved	Preserved	Impaired	Impaired
Fluent (posterior) transcortical	Impaired	Preserved	Impaired	Preserved
Isolation	Impaired	Echolalia	Impaired	No purposeful speech
Anomic	Preserved	Preserved	Impaired	Preserved except for word
Pure word deafness	Impaired only for spoken language	Impaired	Preserved	finding pauses
Pure alexia	Impaired only for reading	Preserved	Preserved	Preserved

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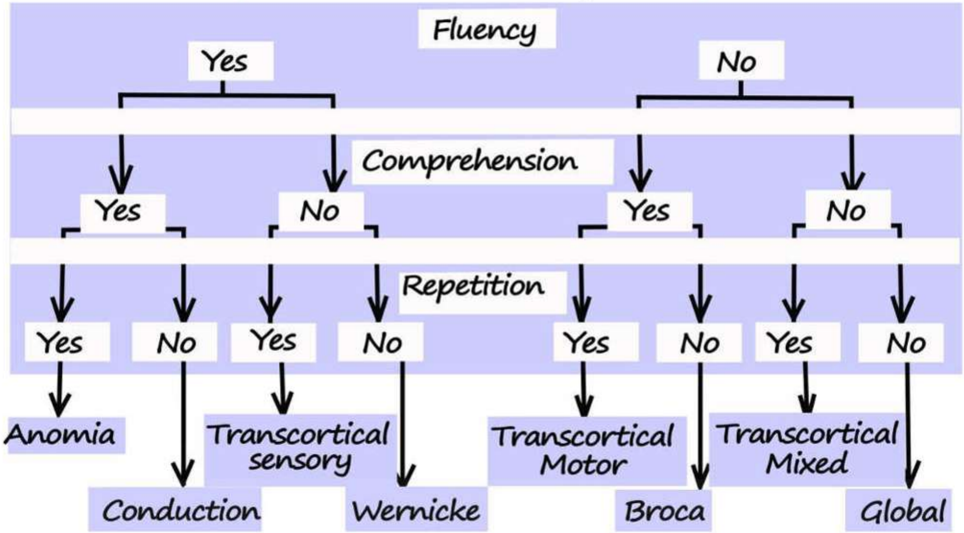
[Classification of the Aphasias]



Subcortical aphasia

- With respect to striatum – striatocapsular aphasia (Broca's)
- With respect to thalamus – thalamic aphasia (Wernicke's)

Apraxia of speech (AOS)

- Difficulty in putting a string of syllables together
- Lesion: - Left interior frontal gyrus (or)

  Left anterior insular region
- Articulatory defect

Dysarthria

- Difficulty in putting a string of same syllables (pa-pa-pa)

Aphemia

- Partial lesion in Broca's area
- Type of speech apraxia
- Acute onset of impaired speech fluency (mutism's) recovery

Dysarthria

- Labial – labial syllables – pa
- Lingual – lingual syllables – ta
- Guttural - ga, ka

Classification of the Dysarthria's			
Type	Localization	Auditory signs	Diseases
Flaccid	Lower motor neuron	Breathy, nasal voice, imprecise consonants	Stroke, myasthenia gravis
Spastic	Bilateral upper motor neuron Unliteral upper motor neuron	Strain-strangle, harsh voice; slow rato; imprecise consonants Consonant imprecision, slow rate. harsh voice quality	Bilateral strokes tumors, primary lateral sclerose Stroke, tumor
Ataxic	Cerebellum	Irregular articulatory breakdowns. excessive and equal stress	Stroke, degenerative disease
Hypokinetic	Extrapyramidal	Rapid rate, reduced bouchons monopitch and monoloudness	Parkinson disease
Hyparkinetic	Extrapyramidal	Prolonged phonemes, variable rate. appropriate sciences, voice stoppages	Dystonia, Huntington disease
spastic and flaccid		Amyotrophic strain-strangle, harsh voce, Dow rata, imprecise consonants	Spastic and flaccid

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- Costic ducarthrin - sullables running into one another
- Upper lateral sclerosis, mut ple strokes
- Spastic dysarthria – syllables running into one another

Cerebellar lesion

- Staccato -undue stress of syllables
- Scanning – undue separation of syllables

Left parental lesion

- Apraxia
- Central alexia
- Acalculia
- Finger anomia
- Right -Left confusion
- Agraphia

(Acalculia, Finger anomia, Right -Left confusion, Agraphia — Gerstman's syndrome)

Right parietal lesions

- Hemineglect
- Constructional apraxia
- Dressing apraxia
- Topographic disorientation

Apraxia

- Inability to perform learned skilled movements on command. With a normal – pyramidal system
  - Extrapyramidal system

- Sensory
- Cerebellar
- Comprehension
- Co-operative

Praxis pathway

- Left parietal lobe (angular gyrus supramarginal gyrus)

↓

is called praxicon – how to use an object

– movement formula

- Left parietal lobe

Left SMA → Right SMA

Left motor area Right motor area → Right & Left UL

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Types

- Conceptual apraxia
  - Do not know what do with the object
- Ideational apraxia
  - Sequencing of events
- Ideomotor apraxia
  - Site of lesion: - SMA
  - Knows what to do, but he cannot do it
  - Difficulty in pantomiming
- Bucco facials apraxia
- Sympathetic apraxia → non dominant limb involved

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Ant part of corpus collosum

- Limb – kinetic apraxia → lesion in pre- motor cortex

  → apraxia of fine skilled movements

Hemineglect

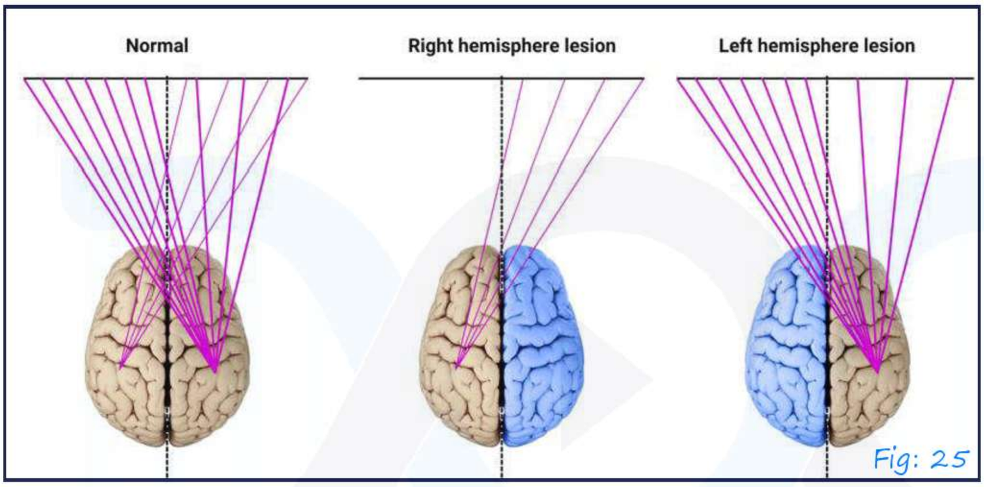


Fig: 25

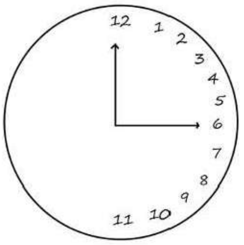
- Letter cancellation test

- Line bisection test →

N

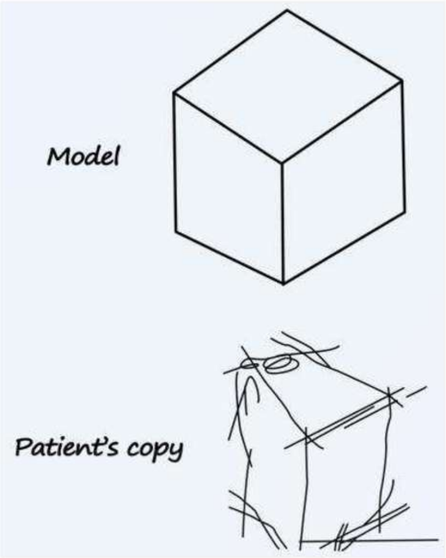
Hemineglect

- Draw a clock



- D/D: – Hemianopia

Constructional apraxia



Graze affection

- Gaze – conjugate movement
- Horizontal gaze → frontal eye filed (area no.8)

↓ Front reticular pathway

PPR 9paraportine reticular formation)

Abducens nucleus

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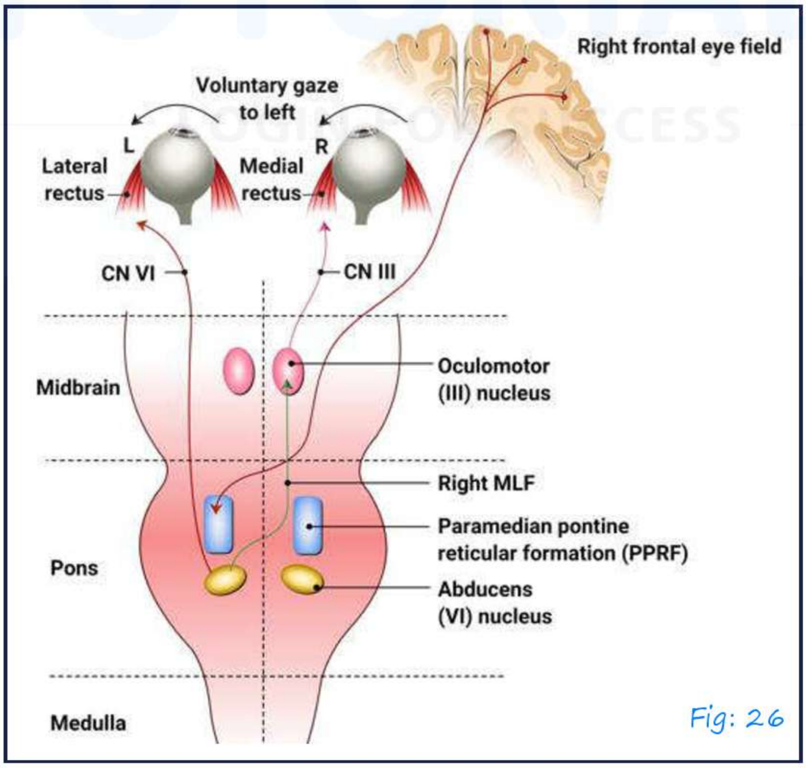

Fig: 26

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- Abducens nucleus consists of 2 types of neurons
  - Fibers of abducens nerve
  - Interneurons → connect by MLF (medial longitudinal fasciculus)
- Right eye field – Right gaze preference / Left gaze palsy
- PPRF- Left gaze preference / Right gaze palsy
- abducens nucleus lesion- Left gaze preferences / Right gaze
- lesion @ MLF alone – I/L adduction deficit
  C/L abduction nystagmus

Fig: 27

- Right PDRF + Right MLF
- 6th nucleus + Right MLF

} ½ syndrome

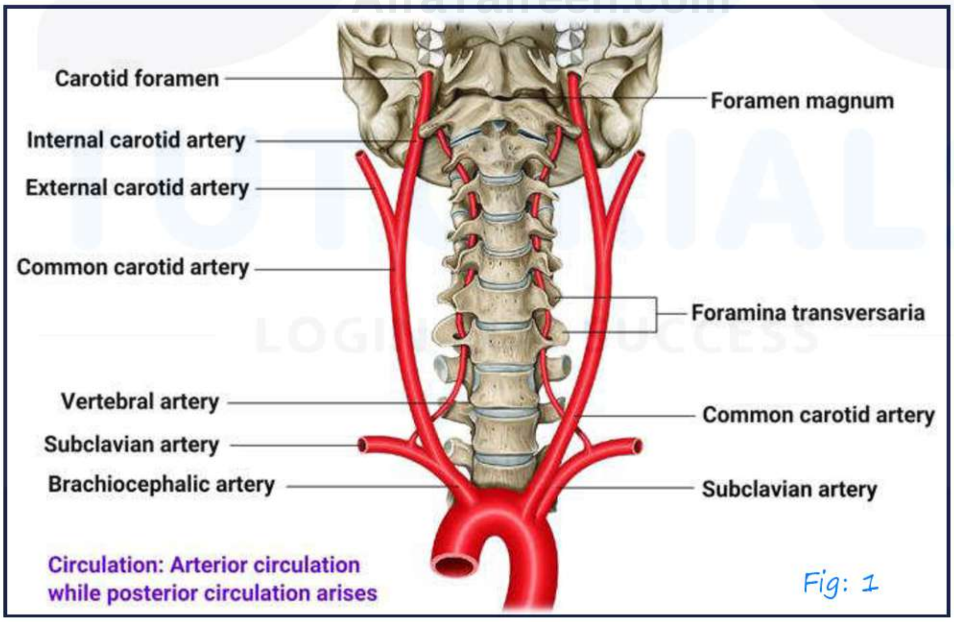
Fig: 28

STROKE SYNDROMES

Stroke syndromes
- Anterior circulation
  - large vessel stroke
  - small vessel stroke
- posterior circulation
  - large vessel stroke
  - small vessel stroke

- Small vessel stroke is also lacunar stroke

Circulation 00:03:07



Circulation: Arterior circulation while posterior circulation arises

Fig: 1

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Stroke syndrome of anterior circulation 00:03:52

- Blood vessels involved
  - MCA
  - ACA
  - Anterior choroidal artery
  - Internal carotid artery
  - Common carotid artery

I. MCA Syndromes

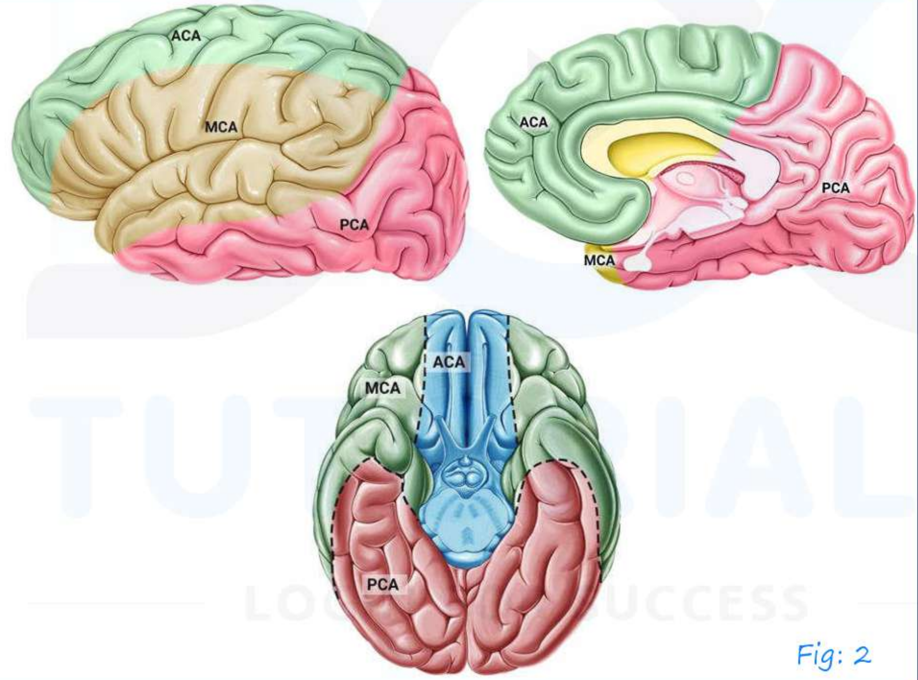

Fig: 2

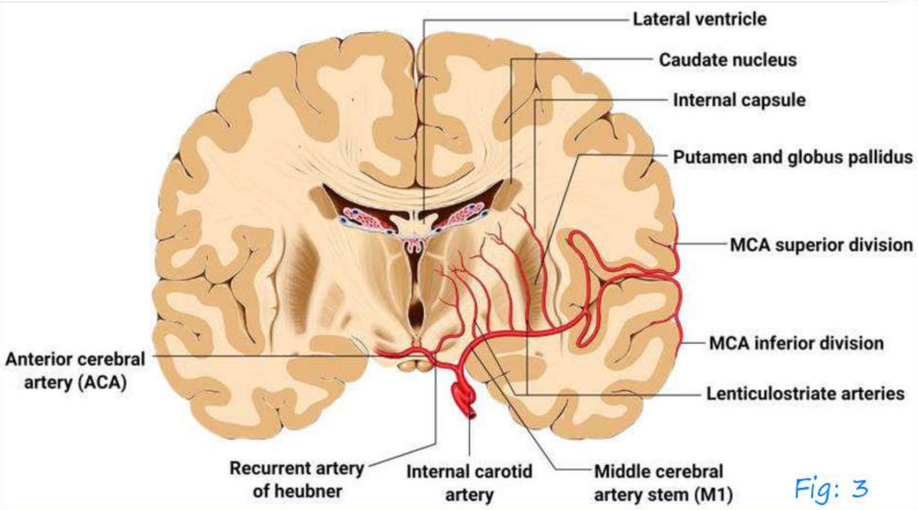

Fig: 3

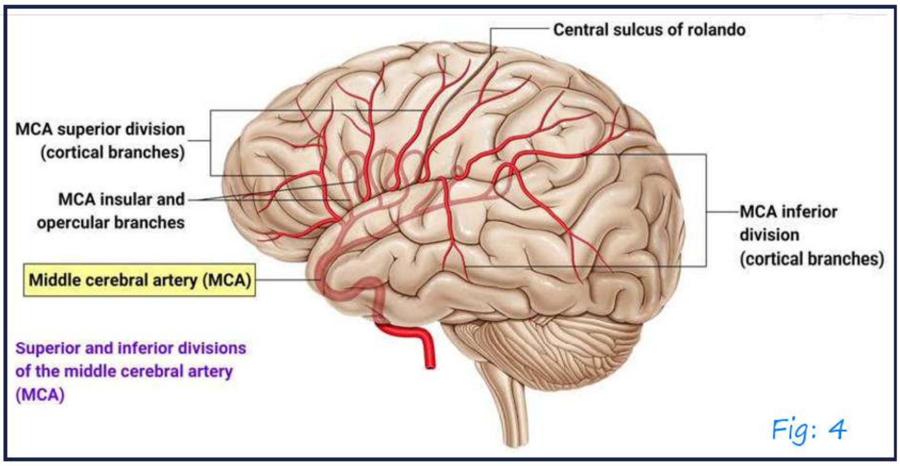

Fig: 4

- Occlusion occurs distally → MCA superior division

↓

Supplies lateral hemisphere

↓

Frontal lobe → Brocca's area parietal lobe

1.Superior division MCA [Dominant]

- Broca's aphasia
- MCA inferior division supplies wernicke's area

2.Inferior division MCA (Dominant)

- Wernicke's aphasia

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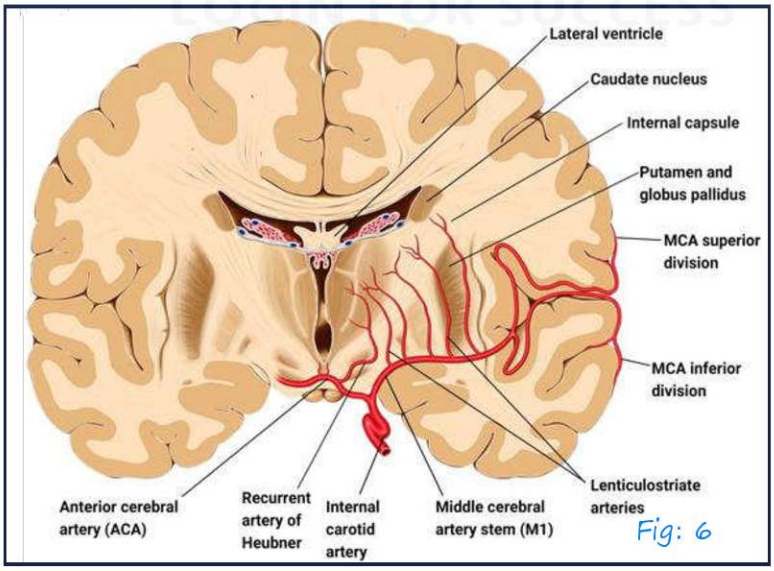

Fig: 6

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3.MCA dominant after lenticulostriate vessel origin

- Global aphasia

4.MCA stem occlusion (dominant)

- Clinical
  - Hemiplegia
  - Hemianesthesia
  - Homonymous hemianopia
- Global aphasia
- Altered level of consciousness
- If frontal eye field is involved → Gaze preference to same side
- Apraxia can also happen as a manifestation of dominant hemisphere involvement
- Dominant parietal lobe involved (Inferior parietal lobule)

↓

Gerstmann syndrome

↓

- Agraphia
- Acalculia
- Finger anomia
- Right – left confusion

5.Lenticulostriate vessel occlusion → small vessel stroke

- Clinical
  - Hemiplegia
  - Hemianesthesia + Dysarthria
  - Homonymous hemianopia

6.MCA stem occlusion (Non dominant hemisphere)

- Classical triad of
  - Hemiplegia
  - Hemianesthesia
  - Homonymous hemianopia
- Dysarthria
- Hemineglect
- Constructional apraxia
- Dressing apraxia
- Visuospatial disorientation
  - Right MCA stroke with gaze preference to right

Fig: 7

  - Territorial infarct pattern

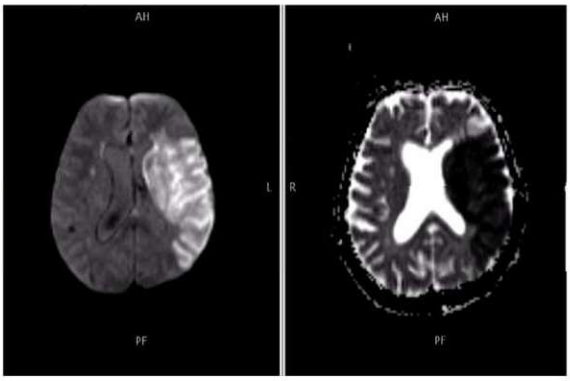

Fig: 8

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- DWI
  - Sequence of choice in acute stroke
  - Bright / Hyperintense → acute stroke
- ADC → dark / hypointense → acute stroke
- Hall mark of acute stroke – diffusion restriction
- Cytotoxic edema occurs in acute stroke
  - Diffusion sequence

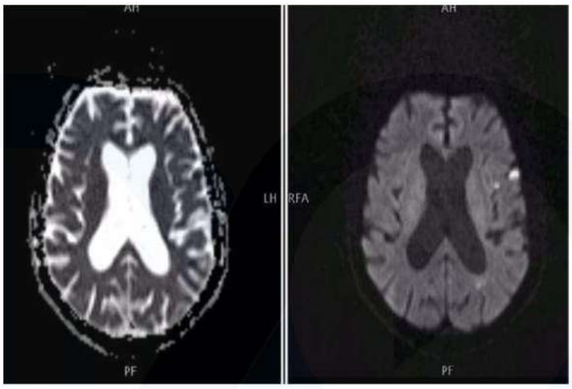

Fig: 9

- T_2 flair axial sequence → superior dix of MCA affected

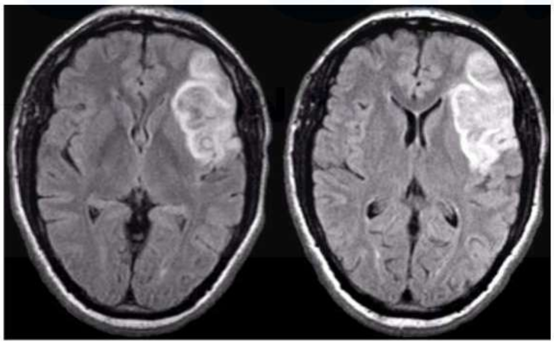

Fig: 10

- T_1
  - Gray → Grey
  - White → White
  - CSF → Dark

- T_2
  - Gray → white
  - White → Grey
  - CSF → White

- T_{2flair}
  - Gray → White
  - White → Grey
  - CSF → Dark

- Diffusion sequences
- Inferior division of MCA involved

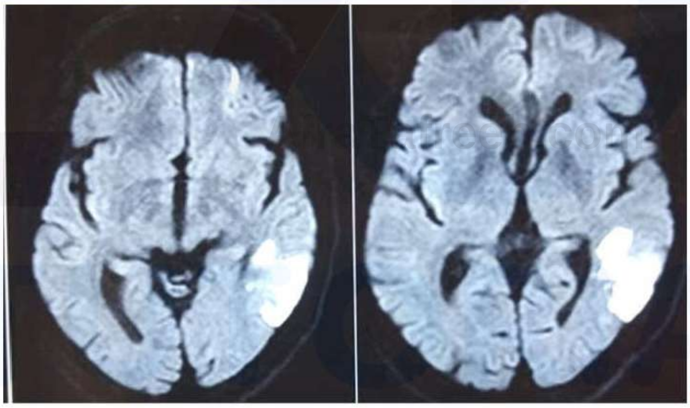

Fig: 11

Fig: 12

- DWI

  Non dominant parietal lobe involvement

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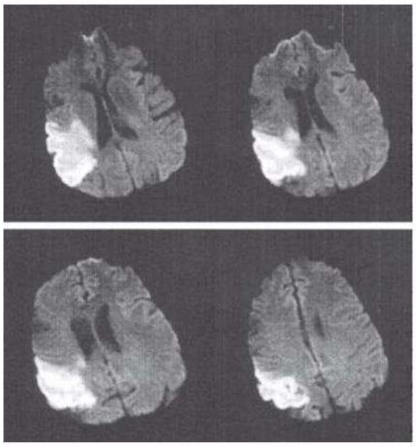

Fig: 13

- GERSTMANN syndrome

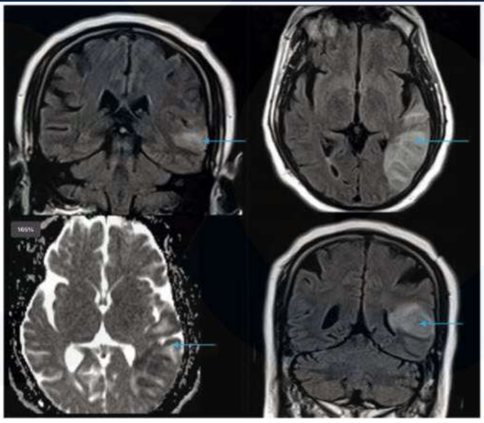

Fig: 14

- DWI → Hyperintensity in internal capsule
- Lacunar stroke

- Charcot's artery – Artery of cerebellar hemorrhage
- Charcot bouchard aneurysm – Aneurysm in lenticulostriate vessels

II.ACA Strokes

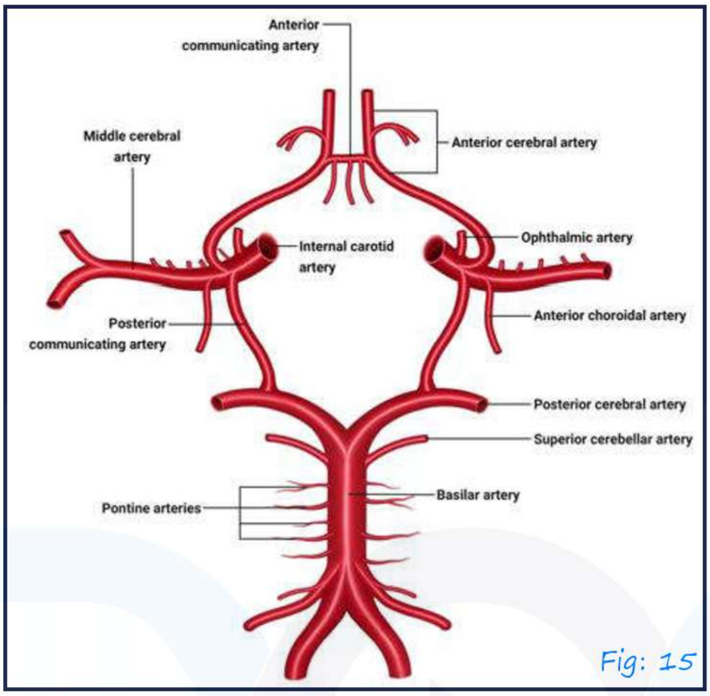

Fig: 15

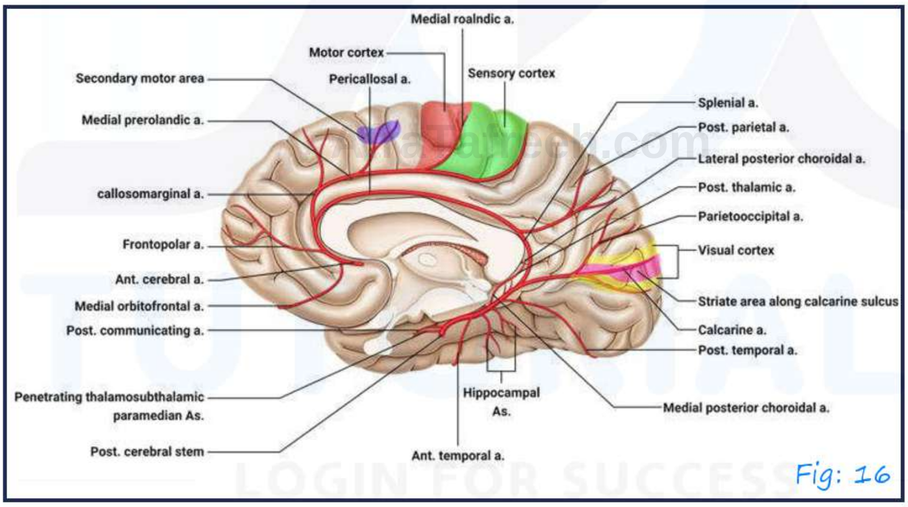

Fig: 16

1.Motor manifestations

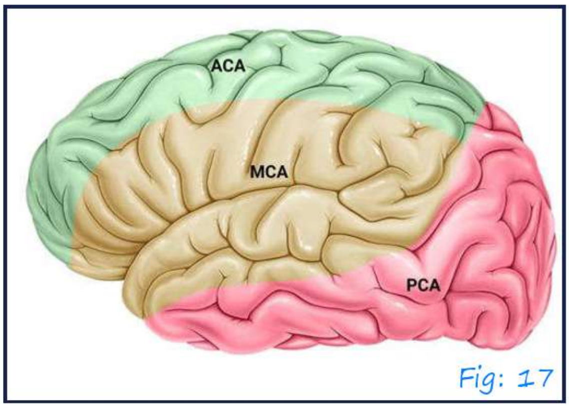

Fig: 17

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- LL Monopareris clinical
- Hemipareris (LL>UL)

2.Sensory

- Cortical sensory loss LL>UL

3.No visual manifestations

4.Bladder manifestations

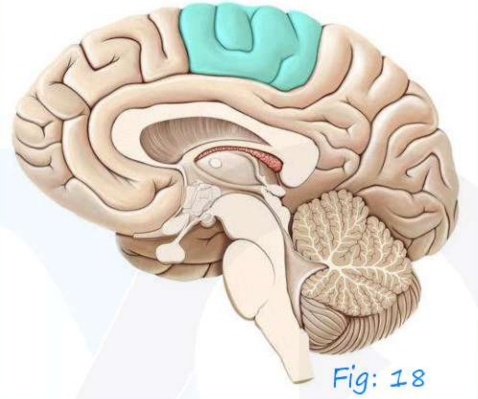

Fig: 18

- Urinary incontinence → paracentral lobule involvement
- Unpaired ACA would cause B/L affection

5.Paratonia / Geganhalten

- Variable resistance to passive movements

6.Abulia – lack of initiation

7.Gait apraxia

8.Sympathetic dyspraxia

Fig: 19

- CT Brain axial view – left ACA infarct

Fig: 20

- Recurrent br of Heuber involved

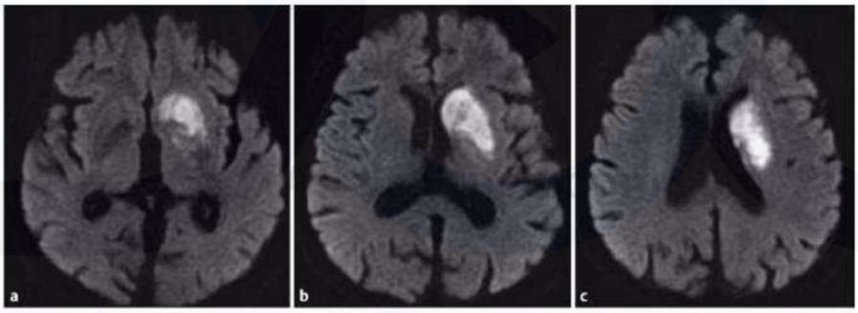

Fig: 21

- Faciobrachial weakness

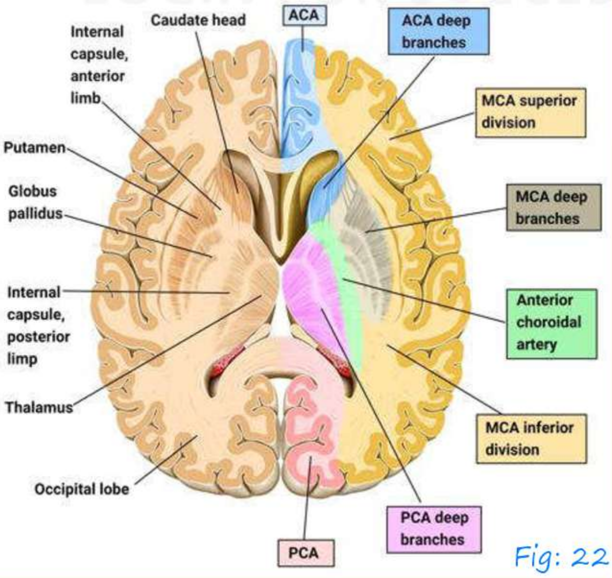

Fig: 22

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III. Anterior choroidal artery

- Supplies posterior limb of internal capsule
- Features: -
  - Classical triad of
    - Hemiplegia
    - Hemianesthesia
    - Homonymous hemianopia

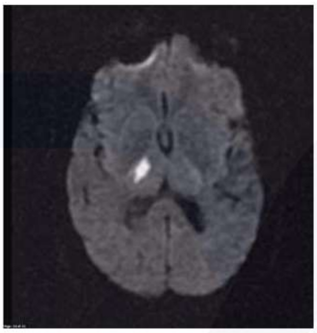

Fig: 23

IV. Internal carotid artery stroke

- Classical triad of
  - Hemiplegia
  - Hemianesthesia
- I/L Blindness

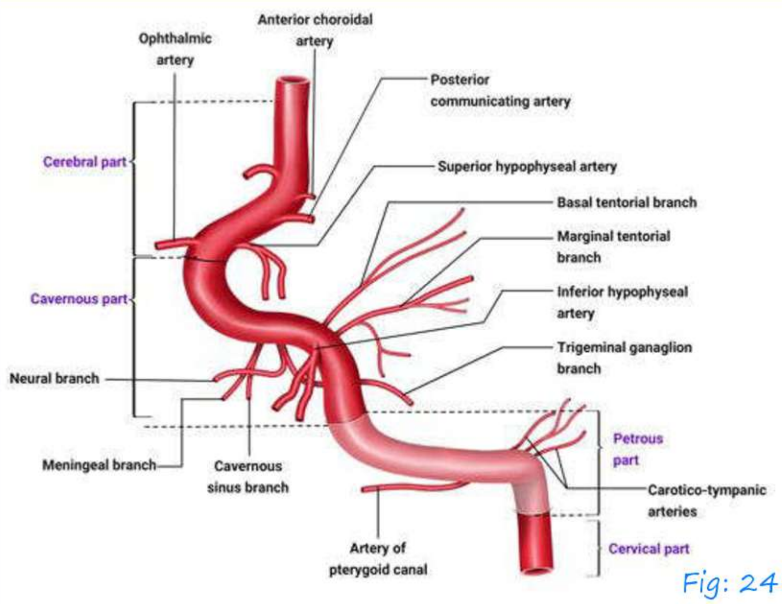

Fig: 24

- Transient monocular blinders – amaurosis fugax

  ↓

  Warning that there is disease in carotids

  HOLLENHORST plaque – cholesterol emboli

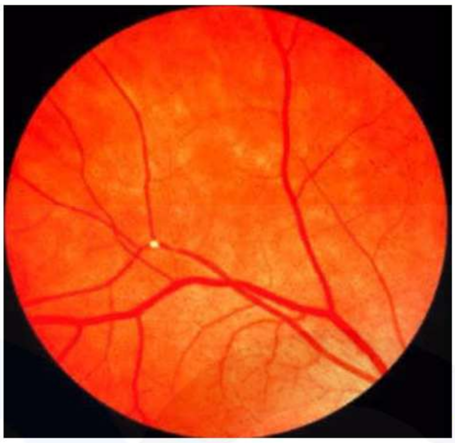

Fig: 25

Posterior circulation stroke 00:55:00

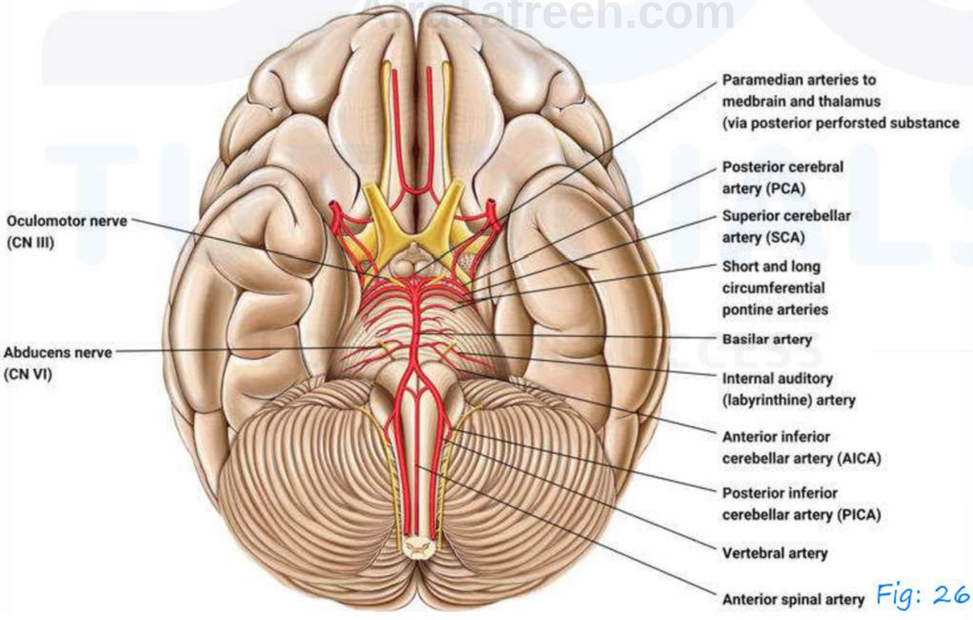

Fig: 26

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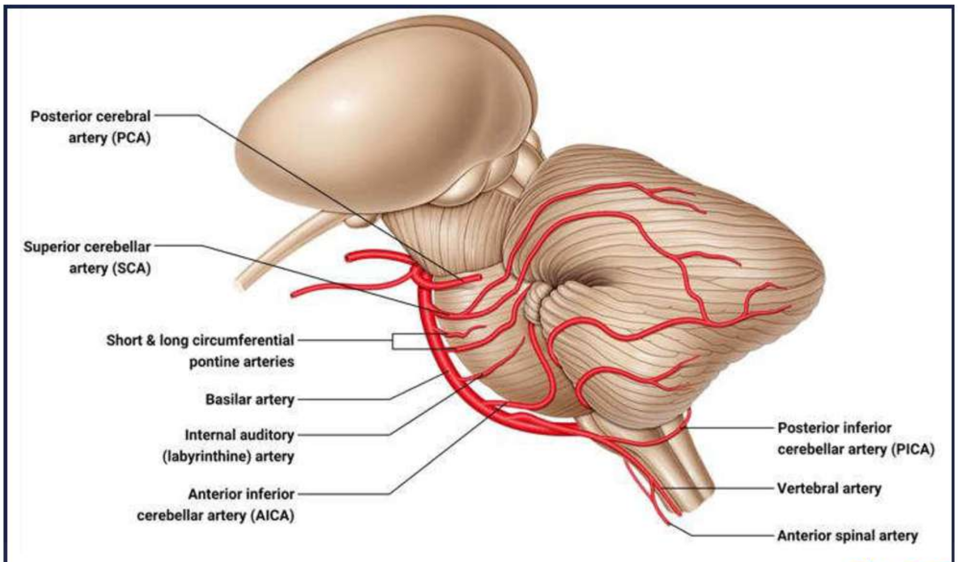


Fig: 27

- Arteries involved
  - Posterior cerebral artery
  - Basilar artery
  - Vertebral artery

1.Posterior cerebral artery

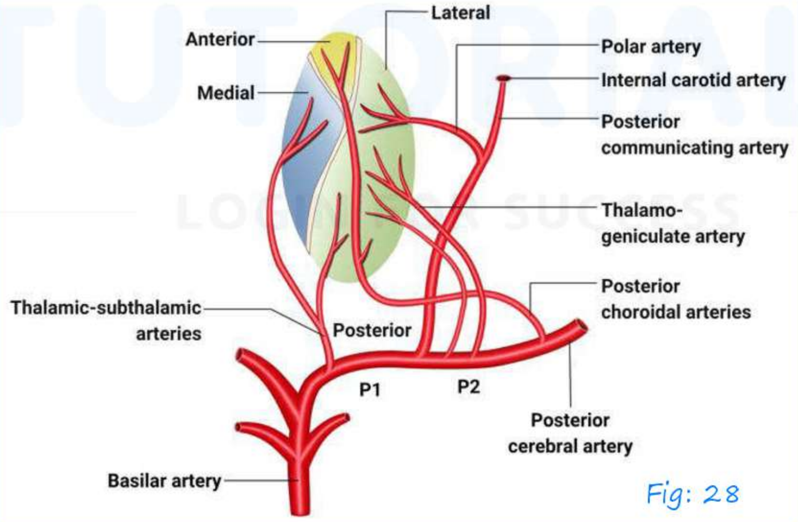
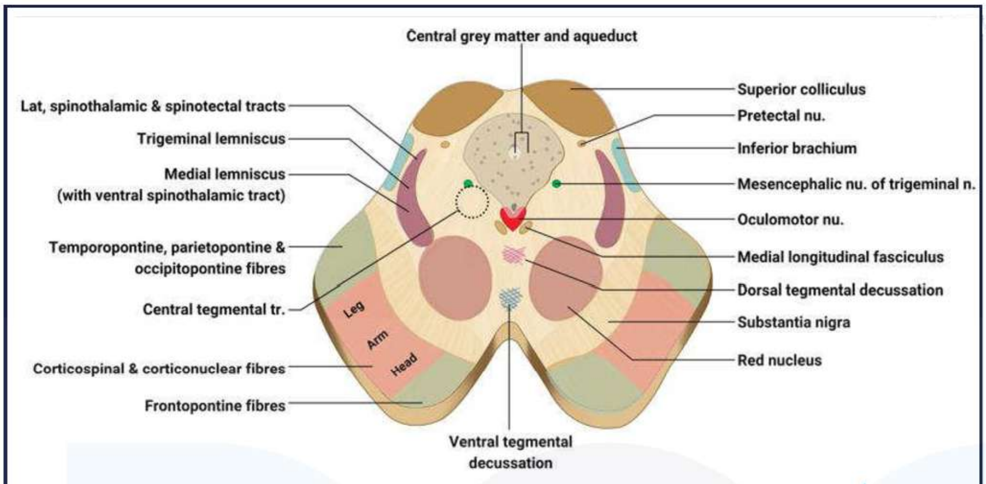


Fig: 28

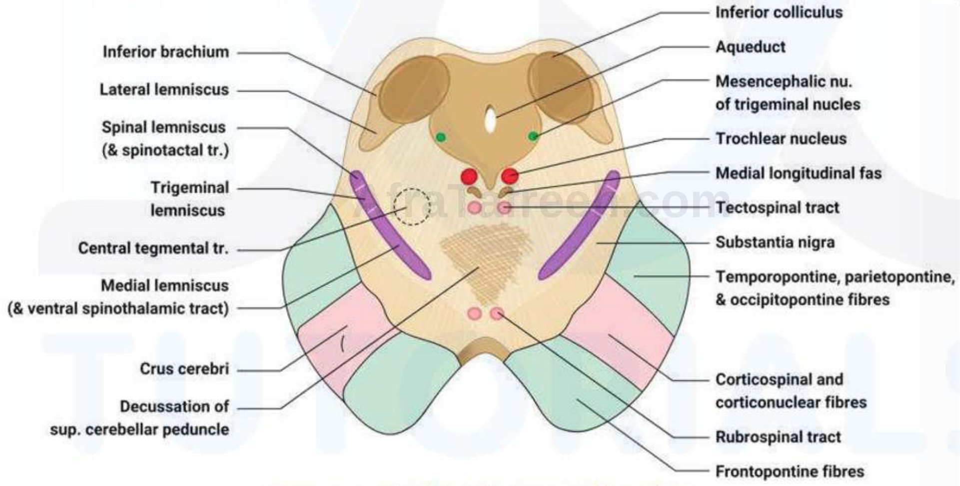
- P_1 Syndromes
  - Structures supplied by P_1 segment
- Thalamus

- Subthalamus
- Midbrain



Transverse section through the uppear part of the midbrain

Fig: 29



Transverse section through the lower part of the midbrain

Fig: 30

- Midbrain syndrome

Syndrome	Lesion Location	Structures Involved	clinical findings
Parinaud's	Midbrain dorsum	Quadrigeminal plate region; pretectum;	Impaired upgaze; convergence retraction

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		periaqueductal gray matter	nystag mus, dilated pupils with light near dissociation.
Weber's	Midbrain base	CN III fibers; cerebral peduncle	Ipsilateral CN III palsy, contralateral hemiparesis.
Benedikt's	Midbrain tegmentum	CN III fibers; red nucleus; CST	Ipsilateral CN III palsy, contralateral hemiparesis with ataxia, hyperkinesia, and tremor ("rubral tremor).
Claude's	Midbrain tegmentum	CN III fibers; red nucleus; SCP	Ipsilateral CN III palsy, contralateral ataxia and tremor ("rubral tremor").
Nothnagel's	Midbrain tectum	Ipsilateral or bilateral CN III	Oculomotor palsies; ataxia

- Parinaud syndrome
  - Lid retraction – Collier's sign
  - Pseudoabducen's palsy
  - Common etiology – pineal gland tumors

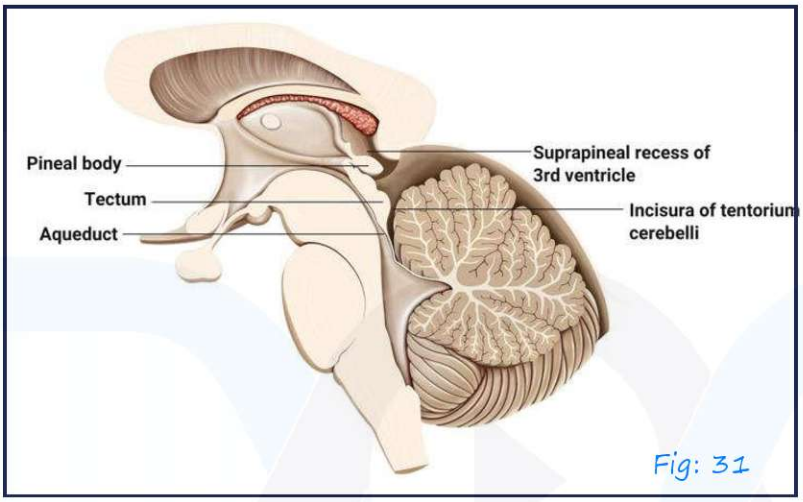

Fig: 31

Fig: 32

  - Skew deviation → vertical malalignment of eyes due to supranuclear lesion
  - Sun setting sign
  - Neurocysticercosis
  - Stroke
- Rubral tremor
  - Frequency < 4 Hz
  - U/L

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- Rest tremor
- Posterior tremor
- Kinetic tremor
- Holmes tremor → Nigrostriatal pathway] Involvement
  → Cerebellar outflow]

- Ataxia: Involvement of cerebellum and its connection

  Superior cerebellar peduncle (SCP)
  Middle cerebellar peduncle
  Inferior cerebellar peduncle

- I/L ataxia
  ↓
  2 exceptions
  - Midbrain
    ↓
    SCP – Dentatorubro – thalamic tract
    ↓
    Decussates at midbrain
  - pons

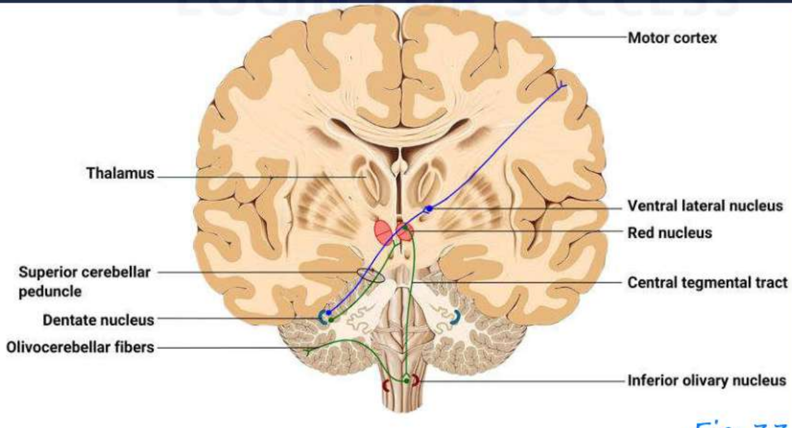

Fig: 33

- Dentatorubro – thalamic tract

lesion before the decussation of midbrain ↓ I/L ataxia	lesion after the decussation ↓ C/L ataxia

- ADP infarct

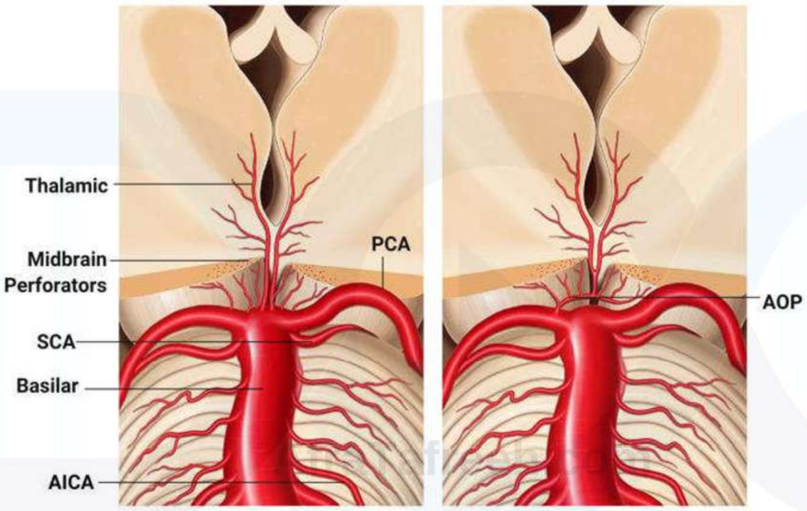

Fig: 34

- Drowsy
- Abulia
- Upgaze palsy

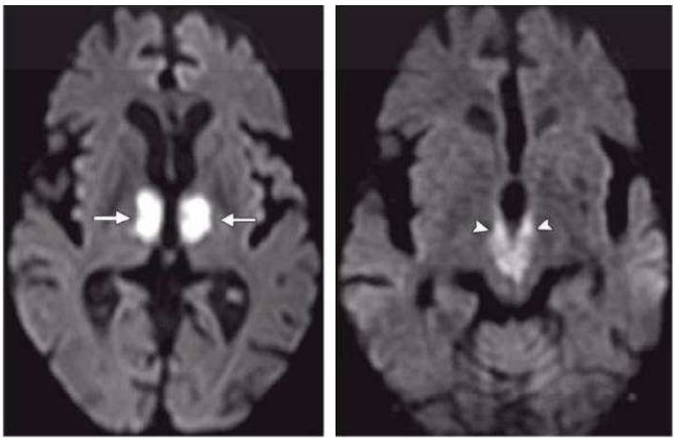
Fig: 35

- Thalamic dejerrine roussy syndrome

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- Lesion involving the venteropostero lateral thalamus
- Severe agonizing pain clinical side

↓

Central neuropathic pain

(or)

Central post stroke pain

- PCOM aneurysm will affect the 3rd ctanial nerve

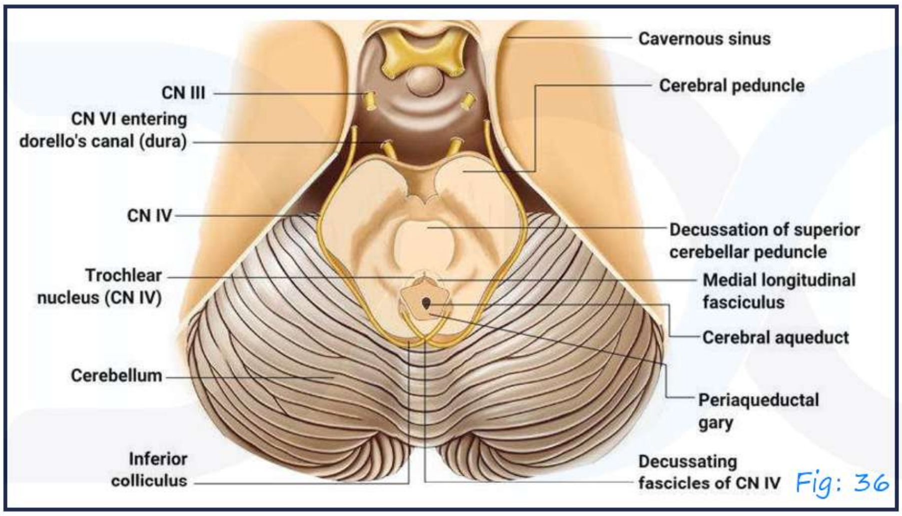

Fig: 36

- CT Brain axial section

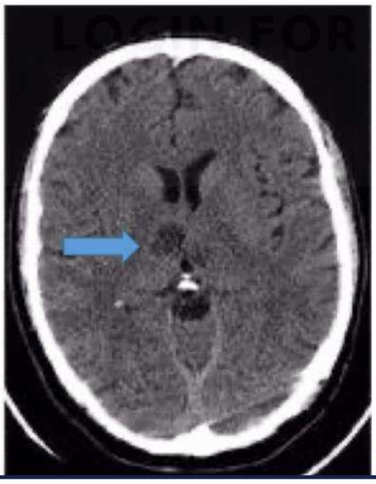
Fig: 37

- Patterns of thalamic infraction

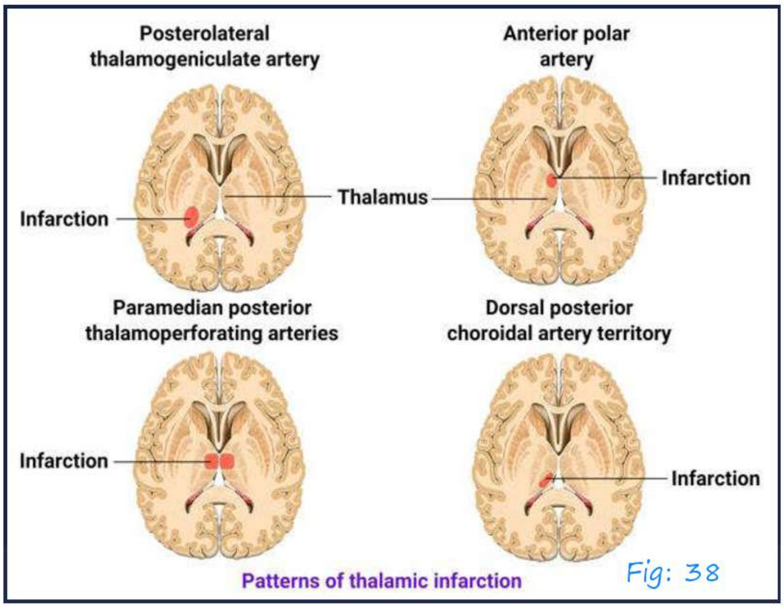

Fig: 38

Stroke syndrome of anterior circulation 00:03:52

- P_2 syndromes
  - Supplies medial temporal lobe occipital lobe

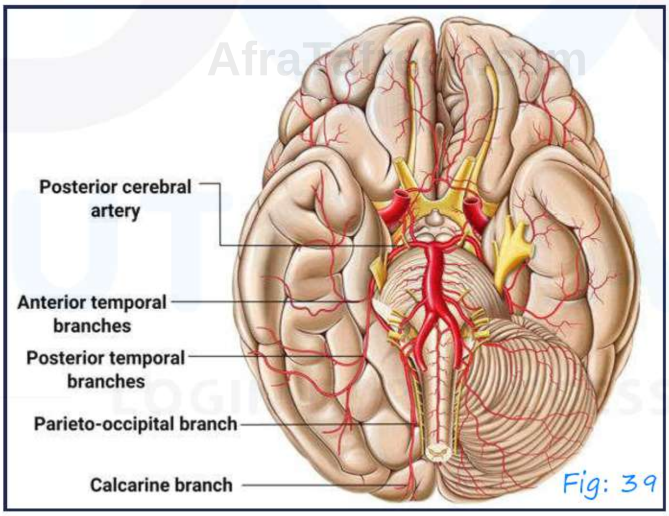

Fig: 39

  - Medial temporal lobe affected → memory disturbances
  - Occipital lobe affected → clinical homonymous hemianopia

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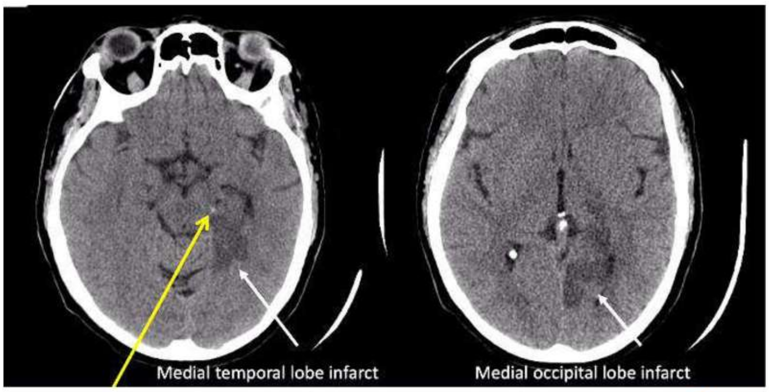

Fig: 40

- B/L distal PCA occlusion → cortical blindness + visual anosognosia

↓↓

Anton's syndrome

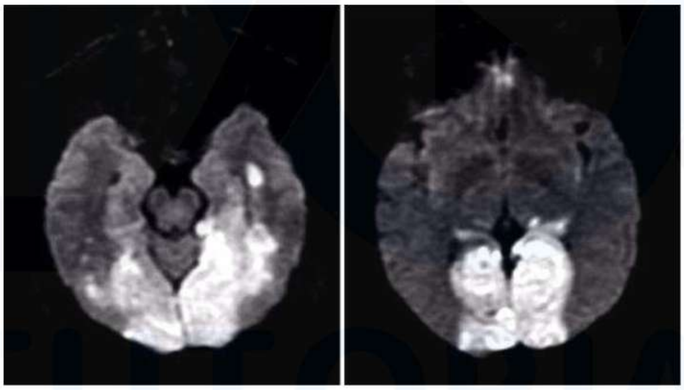
Fig: 41

- Gun barrel type of vision → central part is spared
- Balint's syndrome (Dorsal stream defect) → Due to B/L MCA-PCA infarcts in border zone areas

↓

Seen in cardiac arrest

- Components

1.Optic ataxia → Defective usually guided hand movements

2.Oculomotor apraxia → Defective visual scanning of environment

3.Simultanagnosia → unable to synthesize whole of the image

- Missing the forest for the trees

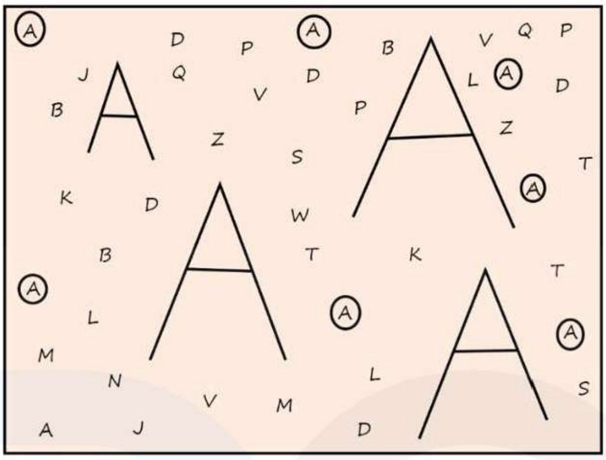

Fig: 42

4.Palinopsia – persistence of visual image even after disappearance of the object

PCA Strokes

↓

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- Peduncular hallucinations colored objects → Hallucinations of brightly

Fig: 43

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- DWI → Lift occipital lobe infarct and splenium of corpus callsoum

↓

Pure alexia

(or)

Alexia without agraphia

2.Basilar artery strokes

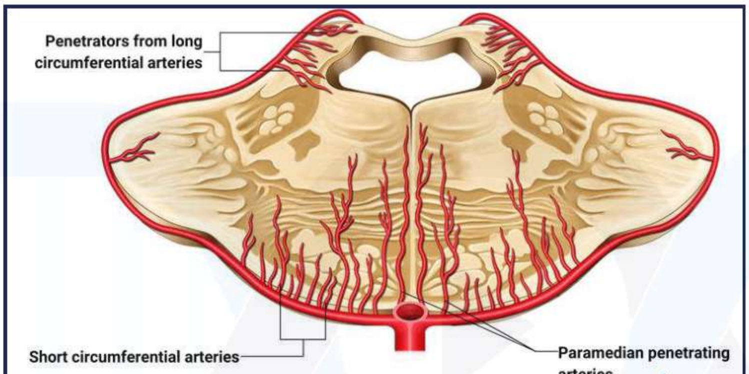

Fig: 44

- B/L Long tract signs
- B/L cranial nerve affection
- Ventral pontine stroke → locked in syndrome (Coma mimic)

↓

Quadriplegia

Horizontal gaze impaired

- Top of basilar stroke

Behavioral state	Definition	Lesion
Locked-in syndrome	Alert and aware, quadriplegic with lower cranial nerve palsy	Bilateral ventral pontine
Persistent vegetative state	Absent cognitive function but retained "vegetative" components	Extensive cortical gray or subcortical white matter with relative preservation of brainstem
Abulia	Severe apathy, patient neither speaks nor moves spontaneously	Bilateral frontal medial
Catatonia	Mute, with marked decrease in motor activity	Usually psychiatric

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Posterior circulation stroke 01:48:58

- Facial colliculus

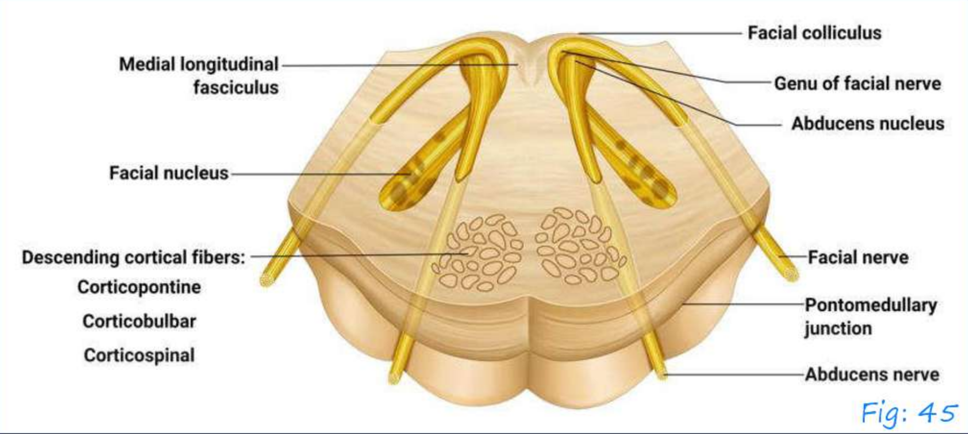

Fig: 45

- Pontine syndromes involving 6th nerve nucleus

Localization (Syndrome)	Ipsilateral abduction palsy (6th nerve lesion)	Ispilateral gaze palsy (6th nerve nucleus lesion)	Contralateral hemiparesis (Corticospinal tract involvement)	Ipsilateral 7th nerve palsy
Ventral and Dorsal Medial Pons (Foville)	No	Yes	Yes	Yes
Dorsal Medial Pons	No	Yes	No	Yes

- Pontine syndromes involving 6th nerve

Localization (Syndrome)	Ipsilateral abduction palsy (6th nerve lesion)	Ispilateral gaze palsy (6th nerve nucleus lesion)	Contralateral hemiparesis (Corticospinal tract involvement)	Ipsilateral 7th nerve palsy
Ventral and Dorsal Medial Pons (Raymond)	yes	no	Yes	no
ventral medial and lateral Pons (Millard-Gubler)	yes	no	yes	yes

- Sectorial supply of PONS

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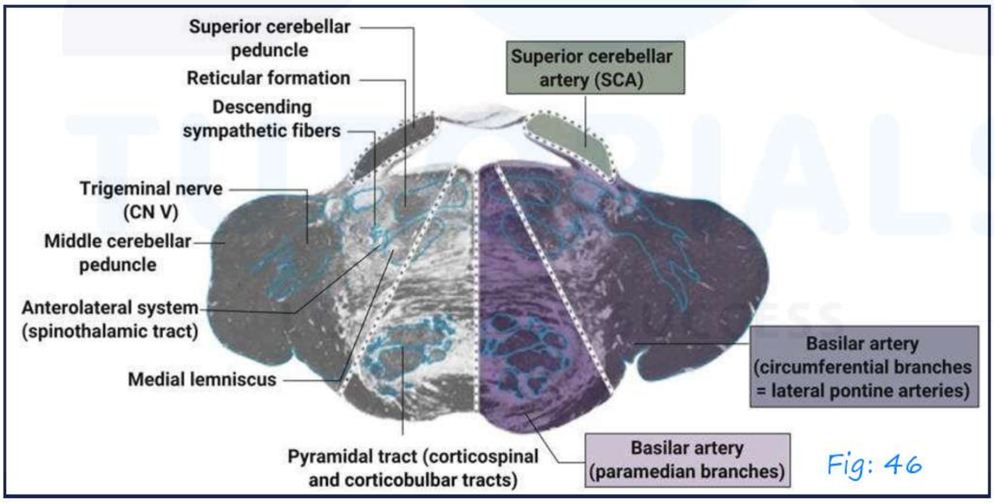

Fig: 46

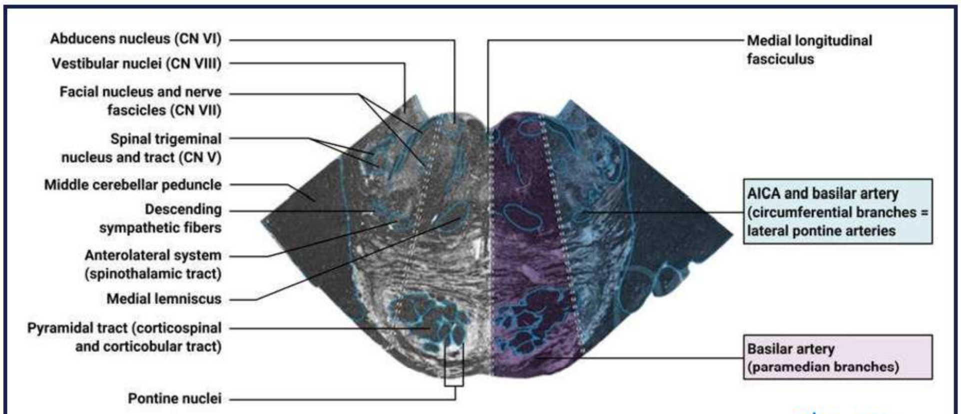

Fig: 47

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- AICA Stroke presents with acute onset deafness due to labrynthine ischemia

Medullary strokes 01:58:19

- Lateral medullary syndrome
- Medial medullary syndrome

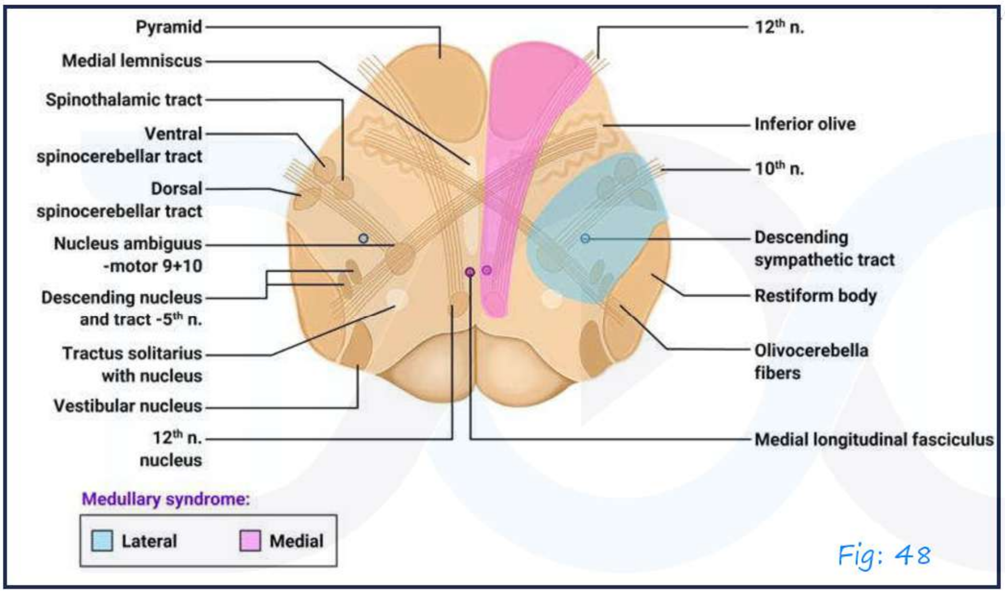

Fig: 48

- Lateral part of medulla
  - Spinothalamic tract
  - Ventral and dorsal Spinocerebellar tract
  - Nucleus ambiguus of 9 and 10
  - Descending nucleus and tract of 5th n
  - Tractus solitarius with nucleus
  - Vestibular nucleus
  - Descending sympathetic tract restiform body
  - Olivocerebellar fibres

- LMS commonly occurs due to vertebral artery occlusion and PICA
- LMS also referred to as PICA syndrome

Wallenberg's (lateral medullary syndrome	Lateral medullary tegmentum	Spinal tract of CN V and its nucleus, nucleus ambiguus, emerging fibers of CNs IX and X, LST, descending sympathetic fibers, vestibular nuclei inferior cerebellar peduncle, afferent spinobarebellar tracts, lateral cuneate nucleus	Loss of pain and temperature of ipsilateral face and contralateral body decreased ipsilateral corneal reflex weakness of ipsilateral soft palate; loss of ipsilateral gag reflex paralysis of ipsilateral vocal cord ipsilateral central Homer's syndrome, mystagmus, cerebellar ataxia of ipsilateral limbs lateropulsion

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- Lateropulsion –inferior olive - vermis

Medial medullary syndrome (Dejerine's anterior bulbar syndrome pyramid hypoglossal syndrome alternating hypoglossal hemiplegia	Medial medulla	XII nucleus or fibers medullary pyramid (At/Near decussation): +/-ML	Ipsilateral toungue weakness contralateral hemiparesis (Sparing the face) +/- Impairment of posterior column function LST functions spared

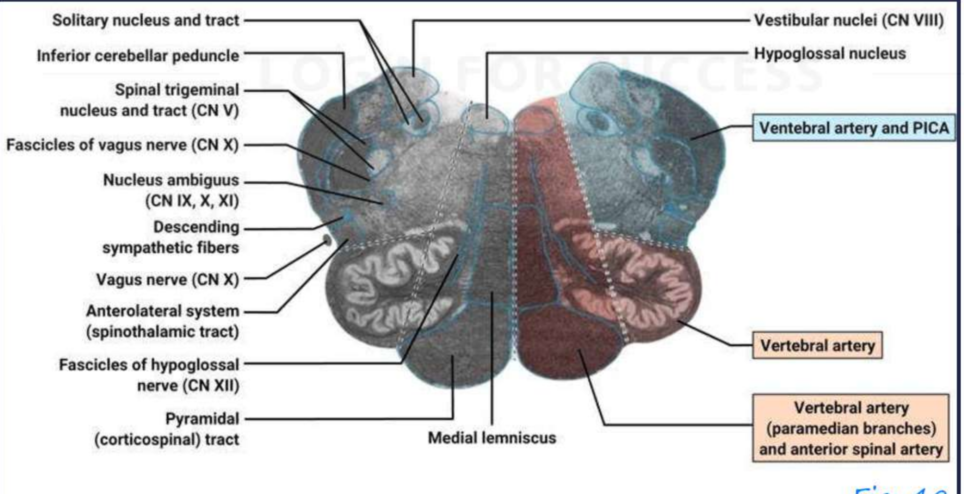

Fig: 49

- DWI → lateral medullary stroke

Fig: 50

- Blood supply of cerebellum

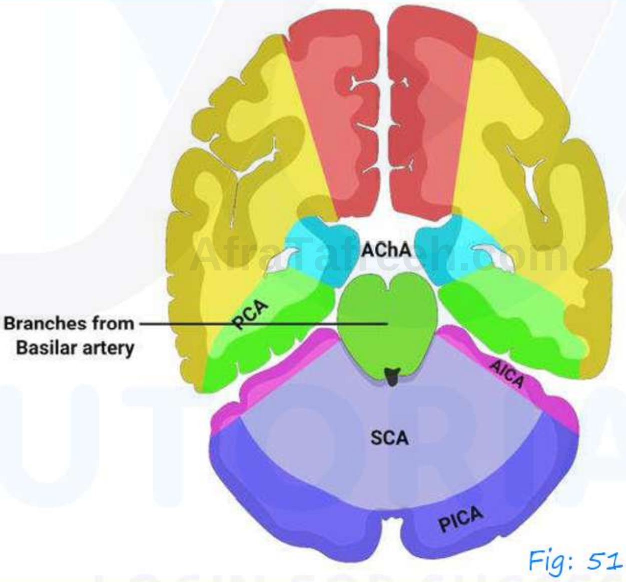

Fig: 51

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MANAGEMENT OF ACUTE ISCHEMIC STROKE

- Patient presents with acute onset of weakness of left UL and LL and deviation of mouth

↓

Is it a stroke?

↓

Yes

↓

Is this patient a candidate for re-vascularisation

↓

Can the penumbra be saved?

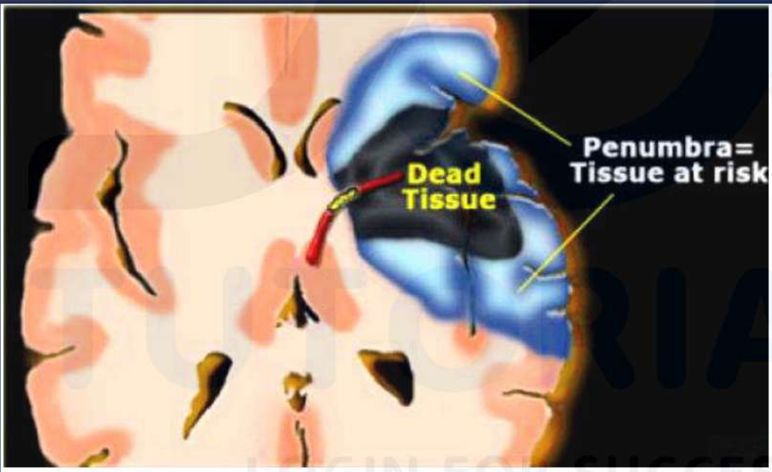

Fig: 1

Revascularization

- Intravenous thrombolysis
  ↓
  - Alteplase (r-tpa)
  - Tenectaplase
- Mechanical thrombectomy
  ↓
  Stent retriever

- Vitals airway breathing circulation → Clinical diagnosis of stroke → ECG Blood sugar → Imaging

- ECG – to look for ischemic changes, arrhythmias
- Hypoglycemia can mimic stroke
- Blood glucose <50

  > 400

  - Thrombolysis should be done within window period (4.5hrs)

↓

Time from stroke onset

  - Wakeup stroke – time when patient was last seen normal

Mechanical Thrombectomy 00:17:03

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- Previously window period for mechanical thrombectomy is 6 hours.
- DAWN, Defuse- 3] Trials → Mechanical thrombectomy can be done 6-24 hours

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Why Imaging 00:18:17

i. Rule out bleed

ii. Rule out stroke mimics

  - Meningioma
  - Ca lung with brain mets
  - CT Brain axial view

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Fig: 2

– Ca lung with hemorrhagic mets

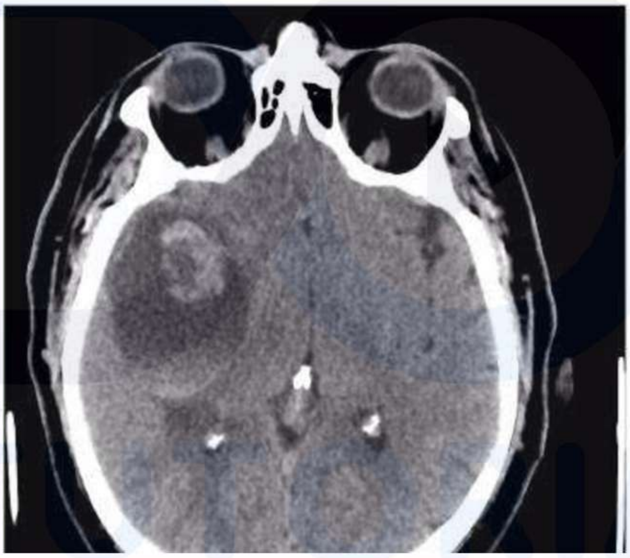

Fig: 3

iii. Candidate for revascularization

Imaging in Acute Stroke 00:22:17

- CT Brain ⎤ Parenchymal imaging
- MRI Brain ⎦

? Vessels → CT angio

MRI angio

- CT Brain in initial 48 hours → Sensitivity is 40-60%
- Normally CT brain does not rule out stroke

- Most sensitive investigation for stroke – DW MRI
  ↓
  - Diffusion restriction
  - Hyperintense DWI
  - Hypointense ADC
- In most scenarios, we go for CT Brain + CT angio

NIHSS Score 00:27:46

- Clinical assessment score
- National Institute of Health Stroke Scale

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Tested Item	Title	Responses and Scores
1A	Level of consciousness	0 - Alert
		1-Drowsy
		2-Obtunded
		3-Coma/unresponsive
1B	Orientation questions (2)	0-Answers both correctly
		1-Answers 1 correctly
		2-Answers another correctly

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1C	Response to commands (2)	0-Performs both tasks correctly
		1-Performs 1 task correctly
		2-Performs neither
2	Gaze	0-Normal horizontal movements
		1-Partial gaze palsy
		2-Complete Gaze palsy
3	Visual fields	0-No visual field defect
		1-Partial hemianopia
		2-Complete hemianopia
		3-Bilateral hemianopia
4	Facial movement	0-Normal
		1-Minor facial weakness
		2-Partial facial weakness
		3-Complete unilateral palsy
5	Motor function	0-No drift

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	a. Left	1-Drift before 10 s
	b. Right	2-Falls before 10 s
		3-No effort against gravity
6	Motor function (Leg)	0-No drift
	a. Left	1-Drift before 5 s
	b. Right	2-Falls before 5s
		3-No effort against gravity
		4-No movement
7	Limb ataxia	0-No ataxia
		1-Ataxia in 1 limb
		2-Ataxia in 2 limbs
8	Sensory	0-No sensory loss
		1-Mid sensory loss
		2-Severe sensory loss
9	Language	0-Normal
		1-Mid aphasia
		2-Severe aphasia
		3-Mute or global aphasia
10	Articulation	0-Normal
		1-Mid dysarthria
		2-Severe dysarthria

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11	Extinction or inattention	0-Absent
		1-Mid loss (1 sensory modality lost)
		2-Severe loss (2 modalities lost)

- Worst score – 42
- Larger score possibly means large stroke

Aspects Score 00:34:59

- Imaging score
- Alberta stroke program early CT score
- Gives some idea about area of involvement

↓

10 areas

- Basal ganglia level
- Supraganglionic level

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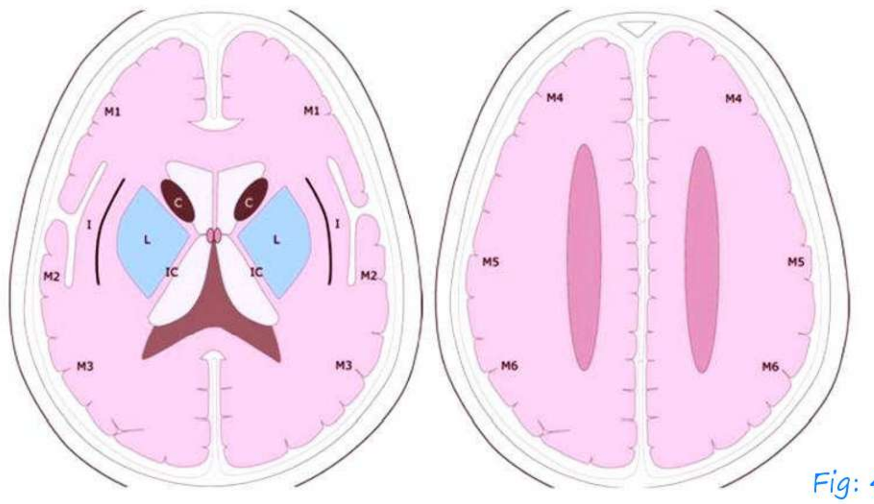

Fig: 4

- CT/MRI
- CT Brain – Hypodensity
- DW MRI – Hyperintensity
- Total score – 10
- No. of areas involved are subtracted from total score of 10

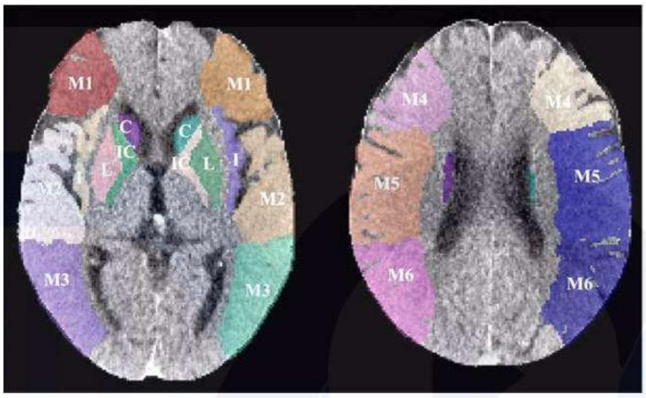

Fig: 5

- Larger stroke – High value of NIHSS
  Low value of ASPECTS

Thrombolysis 00:41:15

AHA/ASA Guideline

- Guidelines for the Early Management of Patients with Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke
- A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association

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American Heart Association Guideline 2019'

00:45:25

Indications

- Diagnosis of ischemic stroke with disabling neurologic deficit (regardless of severity)
- Symptom onset [b] within 4.5 hours
- Wake-up stroke with diffusion-weighted imaging-FLAIR mismatch on MRIC [c]
- Age ≥18 years

Contraindications [d]

- Severe head trauma within 3 months
- Ischemic stroke within 3 months
- Previous intracranial hemorrhage
- Suspected sun arachnoid haaemorrhage
- Suspected IE
- Suspected aortic arch dissection
- Recent brain /spine surgery
- Intracranial intra axial neoplasm
- G.I malignancy/ bleeding
- Active int bleeding
- Bleeding diasthesis
- INR>1.7
- Platelets<100000/mm3
- Bp> 185/110 despite treatment
- Recent LMW heparin
- Use of xa inhibitor

- Acute haemorrhage
- Extensive hypodensity on CT >1/3 of hemisphere
- Diffusion sequence – small lesion
- Flair – large lesion

↓

When there is such a mismatch → penumbra ⊕

Treatment of AIS: IV Administration of Alteplase
Infuse 0.9 mg/kg (maximum dose 90 mg) over 60 min, with 10% of the dose given as a bolus over 1 min.
Admit the patient to an intensive care or stroke unit for monitoring.
If the patient develops severe headache, acute hypertension, nausea, or vomiting or has a worsening neurological examination, discontinue the infusion (if IV alteplase is being administered) and obtain emergency head CT scan.
Measure BP and perform neurological assessments every 15 min during and after IV alteplase infusion for 2 h, then every 30 min for 6 h, then hourly until 24 h after IV alteplase treatment.
Increase the frequency of BP measurements if SBP is >180 mm Hg or if DBP is >105 mm Hg; administer antihypertensive medications to maintain BP at or below these levels.
Delay placement of nasogastric tubes, indwelling bladder catheters, or intra-arterial pressure catheters if the patient can be safely managed without them.
Obtain a follow-up CT or MRI scan at 24 h after IV alteplase before starting anticoagulants or antiplatelet agents.

- Repeat CT scan done 24 hours after thrombolysis
- Antiplatelets → secondary prophylaxis

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Options to treat arterial hypertension in patients with AIS who are candidates for emergency reperfusion therapy

COR IIb	LOE C-EO
Patient otherwise eligible for emergency reperfusion therapy except that BP is >185/110 mm Hg:	
Labetalol 10-20 mg IV over 1-2 min, may repeat 1 time; or	
Nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5-15 min, maximum 15 mg/h; when desired BP reached, adjust to maintain proper BP limits; or	
Clevidipine 1-2 mg/h N, titrate by doubling the dose every 2-5 min until desired BP reached; maximum 21 mg/h	
Other agents (example: hydralazine, enalaprilat) may also be considered	
If BP is not maintained ≤185/110 mm Hg, do not administer alteplase	
Management of BP during and after alteplase or other emergency reperfusion therapy to maintain BP $180/105 mm Hg:	
Monitor BP every 15 min for 2 h from the start of alteplase therapy, then every 30 min for 6 h, and then every hour for 16 h	
If systolic BP >180-230 mm Hg or diastolic BP >105-120 mm Hg:	
Labetalol 10 mg IV followed by continuous IV infusion 2-8 mg/min;	
Nicardipine 5 mg/h N, titrate up to desired effect by 2.5 mg/h every 5-15 min, maximum 15 mg/h; or	
Clevidipine 1-2 mg/h IV, titrate by doubling the dose every 2-5 min until desired BP reached; maximum 21 mg/h	
If BP not controlled or diastolic BP >140 mm Hg, consider IV sodium nitroprusside	

Management of symptomatic intracranial bleeding occurring within 24 hours after administration of IV Alteplase for treatment of AIS	
COR IIb	LOE C-EO
Stop alteplase infusion	
CBC, PT (INR), aPTT, fibrinogen level, and type and cross-match	
Emergent nonenhanced head CT	
Cryoprecipitate (includes factor VIII): 10 U infused over 10-30 minutes (onset in 1 hour, peaks in 12 hour); administer additional dose for fibrinogen level of <150 mg/dL	
Tranexamic acid 1000 mg IV infused over 10 min OR ε-aminocaproic acid 4-5 g over 1 h, followed by 1 g IV until bleeding is controlled (peak onset in 3 hour)	
(Potential for benefit in all patients, but particularly when blood products are contraindicated or declined by patient/family or if cryoprecipitate is not available in a timely manner.)	
Hematology and neurosurgery consultations	
Supportive therapy, including BP management, ICP, CPP, MAP, temperature, and glucose control	

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- Increases ICP → Mannitol
  → 3% saline
  → 30° propped up position
  → Hyperventilation

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Management of Orolingual Angioedema Associated with IV Alteplase Administration for AIS	
COR IIb	LOE C-EO
Maintain airway	
Endotracheal intubation may not be necessary if edema is limited to anterior tongue and lips.	
Edema involving larynx, palate, floor of mouth, or oropharynx with rapid progression (within 30 min) higher risk of requiring intubation.	
Awake fiberoptic intubation is optimal. Nasal-tracheal intubation may be required but poses risk of epistaxis after IV alteplase. Cricothyroidotomy is rarely needed and also problematic after IV alteplase.	
Discontinue IV alteplase infusion and hold ACE inhibitors	
Administer IV methylprednisolone 125 mg Administer iv diphenhydramine 50 mg Administer ranitidine 50 mg iv /famotidine 20 mg iv Epinephrine if angioedema increases Icabitant-for angioedema	

Comparison of pharmacokinetic and pharmacodynamic properties of alteplase and tenecteplase

Properties	TPA	TNK
Fibrin specificity	++	+++
Thrombolytic potency	+	+++
PAI-1 resistance	-	++
Fibrinogen depletion	++	+
PRT activity	++	+++
Clearance (ml/kg/min)	16.1	1.9

- PAI – Plasminogen Activator Inhibitor

Administration of Intravenous Recombinant Tissue Plasminogen Activator (rtPA) for Acute Ischemic Stroke (AIS)"	
INDICATION	**CONTRAINDICATION**
Clinical diagnosis of stroke Onset of symptoms to time of drug administration ≤4.5 hb CT scan showing no hemorrhage or edema of >1/3 of the MCA territory Age 18 2 years	Sustained BP >185/110 mmHg despite treatment Bleeding diathesis Recent head injury or intracerebral hemorrhage Major surgery in preceding 14 days Gastrointestinal bleeding in preceding 21 days Recent myocardial infarction

- Recent MI not a C/I

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Mechanical Thrombectomy 01:16:36

- Stent retriever
- Aspiration device
  - CT angio – axial view

    ↓

  M_1 segment occlusion

Fig: 6

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- <4.5hrs → IV rtPA
  ↓
  Not effective for proximal occlusions

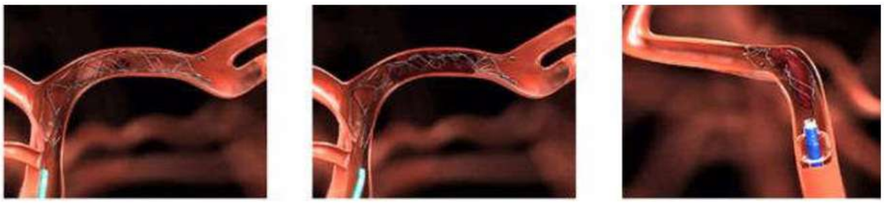
Indications of mechanical thrombectomy

3.7.2.0 to 6 Hours from Onset	COR	LOE
1. Patients should receive mechanical thrombectomy with a stent retriever if they meet all the following criteria: (1) prestroke mRS score of 0 to 1; (2) causative occlusion of the internal carotid artery or MCA segment 1 (M1); (3) age 218 years; (4) NIHSS score of 26; (5) ASPECTS of 26; and (6) treatment can be initiated (groin puncture) within 6 hours of symptom onset.	I	A

- MRS: Modified Rankin Score
- LVO: Large Vessel Occlusion

- Classical window period – 6 hours
  - If patient presents with LVO 3 hrs
    ↓
    IV – rtPA

- DAWN
  DEFUSE-3
  ] Trial → Mechanical thrombectomy window period extended from 6-24 hours
  ↓
  CT perfusion
  MR perfusion
  ↓
  If penumbra visible
  ↓
  Mechanical thrombectomy



Solitaire FR Device open within a brain artery. | Solitaire FR Device grasping and disrupting a clot | Solitaire FR Device pulling out (retrieving) a clot

Fig: 7

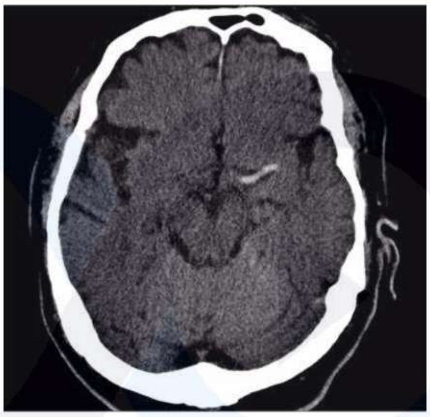


Fig: 8

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- CT Brain axial view

↓

Hyperdense MCA sign

↓

Hyperacute stroke

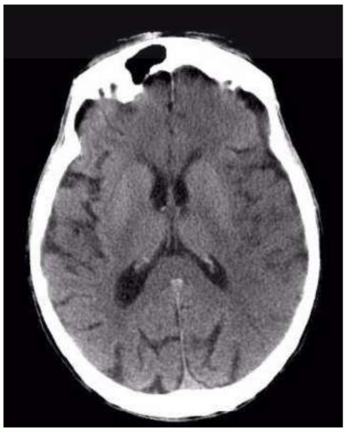

Fig: 9

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- CT brain axial view

↓

Insular cortex – hypodense

↓

Grey white differentiation is lost

↓

Loss of insular ribbon

- Acute stroke
  - >24 hours (or) <24 hours (not a candidate for revascularization procedures)

  Ischemic stroke

  ↓

  - Role for antiplatelet → Aspirin 325 mg loading dose

  Role for anticoagulant → No role

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SECONDARY PROPHYLAXIS OF STROKE

Secondary prophylaxis of stroke 00:01:54

- Antiplatelet
- Anticoagulant
- Optimal management of vascular risk factors → T_2 DM
  HTN
  Dyslipidemia
- Lifestyle modifications

Antiplatelets 00:01:54

- Aspirin
- Clopidogrel
- Ticagrelor
- Prasugrel
- Cilastazole → PDE – 3 inhibitors

1. Aspirin: –
    - Gold standard antiplatelet
    - Targets COX – 1 and decreases production of T_XA_2
2. Clopidogrel: – Targets P_2Y_{12} receptor
    - Aspirin superior to clopidogrel
3. Dipyridamole: – interferes with adenosine reuptake
    - Dose: –
        - Aspirin: – 150mg daily
        - Clopidogrel: – 75mg daily

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- In general, single antiplatelet preferred over dual antiplatelet in certain exceptions
- Dual antiplatelets given in
  - TIA and minor stroke (21 days f/b single antiplatelet)
  - Symptomatic intracranial stenosis
  - Unstable extracranial plaque
- Neck vessel doppler → ulcerated plaque → dual antiplatelets

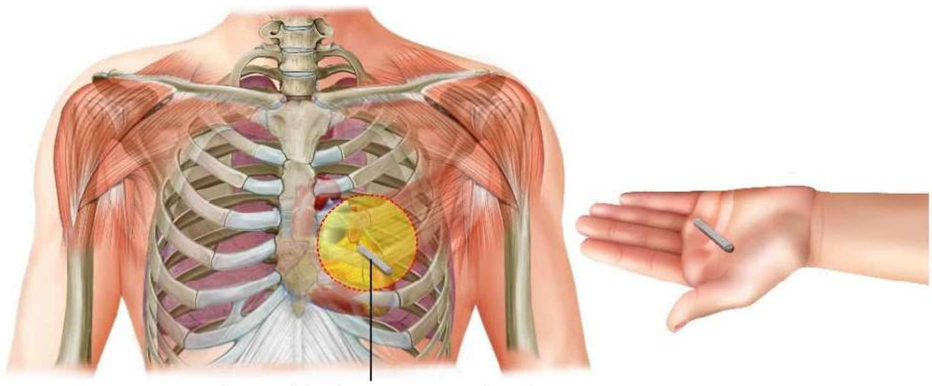
  Co-existing CAD
- Lifelong antiplatelets treatment

Anticoagulants 00:22:18

- Given in cardioembolic stroke
- Warfarin – 70% protection
- Aspirin – 20% protection
- Most common cause of cardioembolic stroke: - NVAF
  - Anticoagulants started 4-14 days after acute ischemic stroke (ASA guidelines)

Rate of AF detection
• Single ECG: 2.7% • Holter monitor 24 hours: 3.2-4.8% • Holter monitor 48 hours: 6.4% • Holter monitor 7 days: 12.5%

- Most common AF: - paroxysmal



Implantable loop recorder is placed under the skin

Fig: 1

Fig: 2

Transesophageal echo
• Atrial thrombus • Atrial appendage thrombus • Atrial myxoma • Atrial septal aneurysm • Atrial septal defect • PFO • Aortic arch atheroma • Mitral valve vegetations

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- Rheumatic AF: - oral anticoagulants (OAC)
- Prosthetic valve AF: - OAC
- Non valvular AF → CHA_2DS_2 VAS scoring

letter	Risk factor	Score
C	Congestive heart failure/LV dysfunction	1.
H	Hypertension	1
A_2	Age 275	2
D	Diabetes mellitus	
S_2	Stroke/TIA/thrombo-embolism	
V	Vascular disease	1
A	Age 65-74	1
S	Sex category (ie, female sex)	1
	Maximum score	9

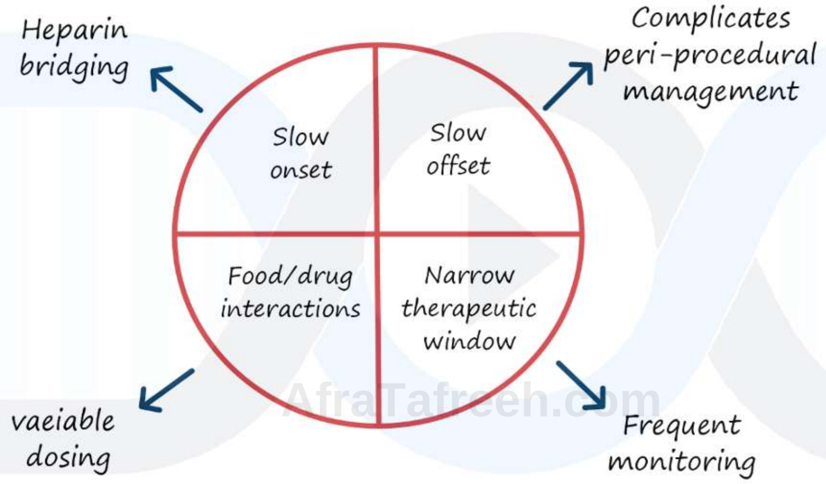
Congestive heart failure/LV dysfunction means LV ejection fraction 40% Hypertension includes the patients with current antihypertensive medication. "Prior myocardial infarction, peripheral artery disease, aortic plaque. LV: left ventricular, TIA: transient ischemic attack

- CHA_2DS_2 VAS score
  - 0 → antiplatelets
  - 1 → OAC/antiplatelets
  - ≥ 2 → OAC
- Drugs: -
  - Warfarin

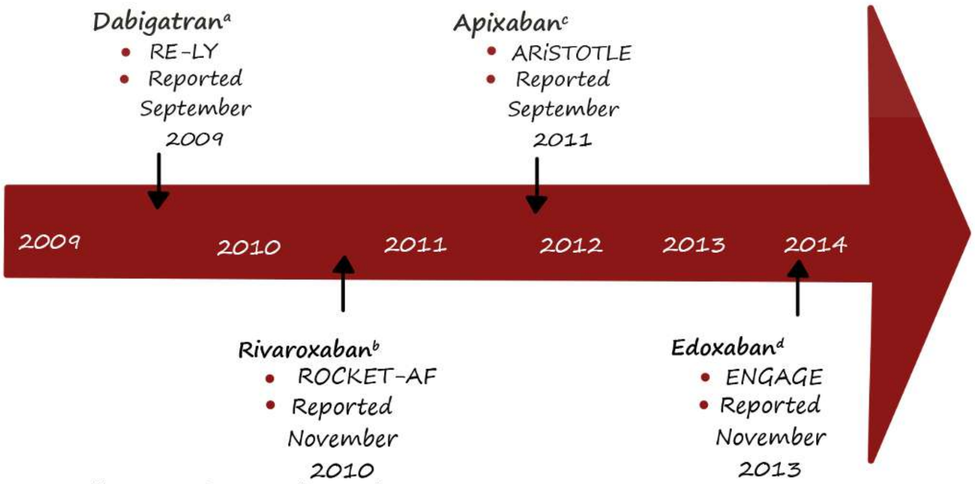
- NOAC
  - i. Dabigatran (direct thrombin inhibitor)
  - ii. Ximelagatron (direct thrombin inhibitor)
  - iii. Apixaban
  - iv. Rivaroxaban
  - v. Edoxaban

  (iii–v: factor X a inhibitor)

Limitation Of Warfarin



Novel Anticoagualants for Stroke Prevention in Atrial Fibrillation



a. Connolly SJ. et al. N Engl J Med. 2009:361:1139-1151.
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Advantages of New Oral Anticoagulants Over Warfarin		
Feature	**Warfarin**	**New Orals**
Onset	Slow	Rapid
Dosing	Variable	Fixed
Food effect	Yes	No
Interactions	Many	Few
Monitoring	Yes	No
Offset	Long	Short

Vitamin K Antagonistand Direct Oral Anticoagulan					
Property	Warfarin	Rivaro xaban	Dabigatran	Apixaban	Edoxaban
Mechanism	Vitamin K antagonist	Factor Xa inhibit or	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Typical dose for atrial fibrillation	Variable	20 mg daily	150 mg 2 times a day	5 mg 2 times a day	60 mg daily
Renal dose adjustment	No	Yes	Yes	Yes	Yes
Half-life	20-60 hours	5-9 hours	12-17 hours	-12 hours	8-10 hours
Onset of action	24-72 hours	3-4 hours	0.5-2 hours	3-4 hours	1-2 hours

- Recurrent AF: - watchman device

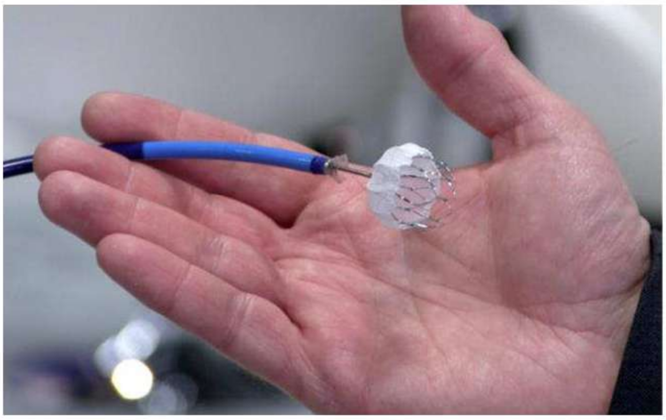

Fig: 3

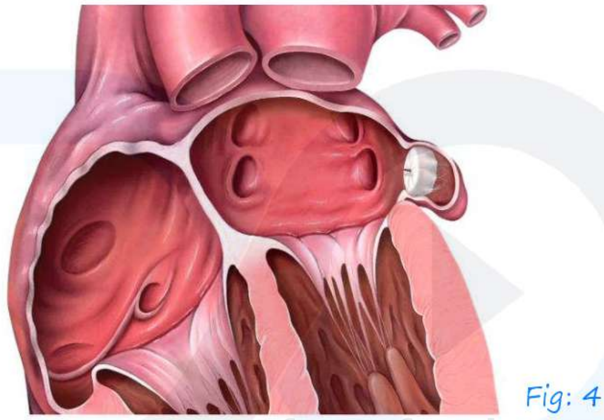

Fig: 4

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Patent formen ovale treatment
• Antiplatelet • Oral anticoagulant • PFO closure

- PFO: - 1 in 4 normal population
- 2020 – guidelines → PFO closure > medical management

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Management of vascular atherosclerosis in large artery Stroke 00:34:45

- Large artery atherosclerosis (LAA)
  - Intracranial
- Symptomatic
- Asymptomatic
  - Extracranial
- Symptomatic
- Asymptomatic

Extracranial LAA

- Symptomatic ≥ 50%

Surgical endovascular

Medical management

- Surgical → CEA [carotid endarterectomy]

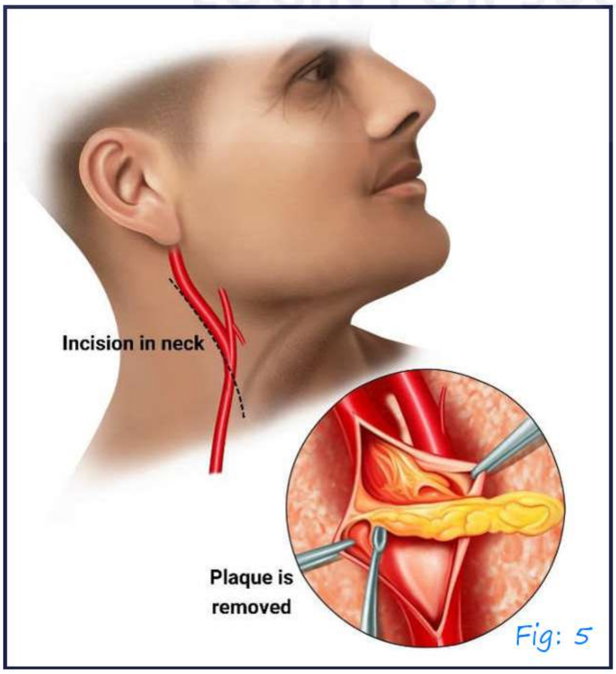

Fig: 5

- Endovascular → angioplasty – balloon /stent

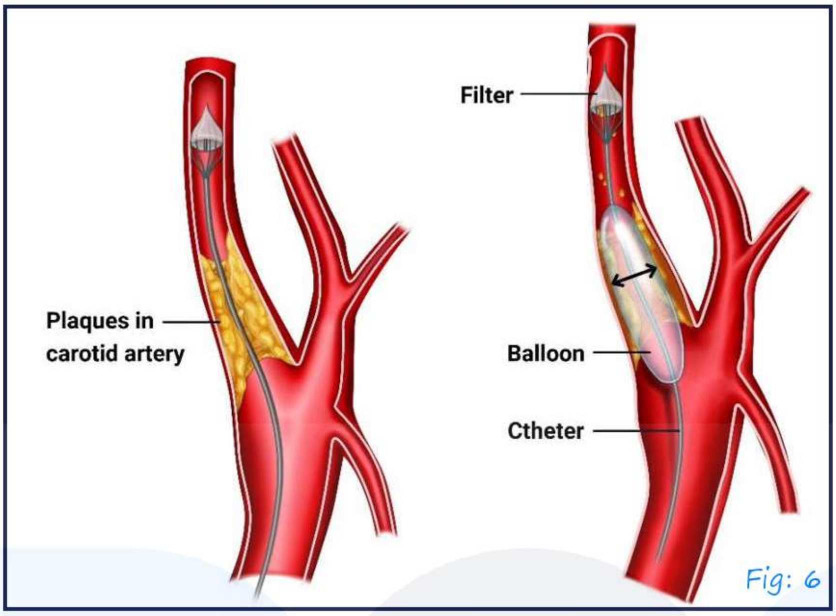

Fig: 6

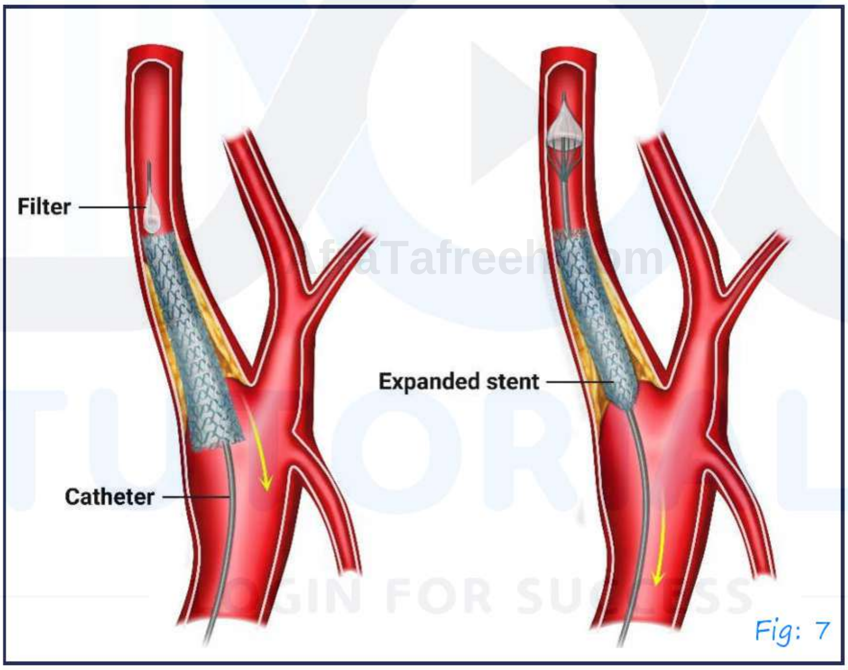

Fig: 7

- Surgical > endovascular
  - NASCET Trial
  - ECST Trial
- Asymptomatic
  - Medical > procedure
  - Antiplatelets
  - Statins

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- Management of vascular risk factors
- Lifestyle modification

Intracranial LAA

- Medical > procedure.

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TRANSIENT ISCHEMIC ATTACKS (TIA)

Introduction 00:00:54

- Type of Stoke, duration <24 hours (NIHES → 0)
  (Time Based definition)
  ↓
- Tissue based Definition
- If there is any tissue damage, then it is stroke, though the patient has complete recovery
- TIA' vascular insult to Brain, Retina, Cochlea, Spinal cord
- AICA → supplies labyrinth
- Evaluation of TIA – Same as stroke
- Whether to admit? – Yes
- Prognosticate → ABCD2 scoring system

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Risk of stroke following transient ischemic attack: The ABCD2: Score	
Clinical factor	Score
A: Age ≥ 60years	1
B: SBP >140mmHg or DBP >90mmHg	
Unilateral weakness	2
Speech disturbance without weakness	1
D: Duration	
>60min	2
10-59min	1
D: Diabetes (Oral medications or insulin)	1

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Total score	Sum each category
ABCD2 score total	3-month rate of stroke (%)
0	0
1	2
2	3
3	3
4	8
5	12
6	17
7	22

- ABCD2 score ≥ 4 → Very vigilant

Differential diagnosis 00:11:52

- Migraine
- Seizure
- Transient global amnesia
- Amyloid spells

Treatment 00:12:56

- Dual antiplatelet x 21days followed by single antiplatelet.

TRANSIENT GLOBAL AMNESIA

TGA 00:00:35

- Age > 50years
- Vascular risk factors
- Transient episode of Centro grade amnesia
- Recovers in 24hours

Diagnostic criteria

- Attacks must be witnessed
- There must be anterograde amnesia during the attack
- Cognitive impairment is limited to amnesia
- No clouding of consciousness or loss of personal identity
- No focal neurological signs/symptoms
- No epileptic features
- Attack must resolve within 24hours
- No recent head injury or active epilepsy
- Imaging may show diffusion restriction in hippocampus.

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INTRACRANIAL HEMORRHAGE

Intracranial hemorrhage 00:00:12

- Intracerebral hemorrhage (most common)
- Extradural hemorrhage
- Subdural hemorrhage
- Subarachnoid hemorrhage

Etiology 00:01:35

Causes of Intracranial Hemorrhage		
CAUSE	LOCATION	COMMENTS
Head trauma	Intraparenchymal: frontal lobes, antenor temporal lobes: subarachnold: extra-asial (subdural, epidural)	Coup and contrecoup injury duning brain deceleration
Hypertensive hemorrhage	Putamen, globus pallidus, thalamus cerebellar hemisphere, pons	Chronic hypertension produces hemorrhage from small -30-100 pm) vessels in these regions
Transformation of prior ischemic Infarction	Basal ganglion subcortical regions, lobar	Occurs in 1-6% of ischemic strokes with predilection for large hemispheric infarctions
Metastatic brain tumor	Lobar	Lung, choriocarcinoma, melanoma, renal cell carcinoma. thyroid, athal myxoma
Coagulopathy	Any	Risk for ongoing hematoma expansion

Drug	Any, lobar, subarachnoid	Cocaine, amphetamine
Arteriovenous malformation	Lobar, intraventricular, subarachnold	Risk is-2-3% per year for bleeding if previously unruptured
Aneurysm	subarachnoid, intraparenchymal, rarely subdural	Mycotic and nonmycotic forms of aneurysms
Amyloid anglopathy	Lobar	Degenerative disease of Intracranial vessels; associated with dementia, rare in patients <60 years
Cavernous angioma	Intraparenchymal	Multiple cavernous ang omas linked to mutations in KR/T1. CCM2, and POCD10 genes
Dural arteriovenous fistula	Lobar, subarachnoid	Produces bleeding by venous hypertension
Capillary telangiectasias	Usually, brainstem	Rare cause of hemormage

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- Elderly individuals → amyloid deposition → arteriolar degeneration
- Lobar bleeds → amyloid angiopathy

Intracerebral hemorrhage 00:07:24

- HTN
- Trauma
- Drugs
- Coagulopathy

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Clinical Features:

- Headache
- Focal neurological deficit
  - Worsening of sensorium → coma

Investigations:

- CT Brain (plain)
- MRA
- CTA
- coagulation parameters
- platelet count

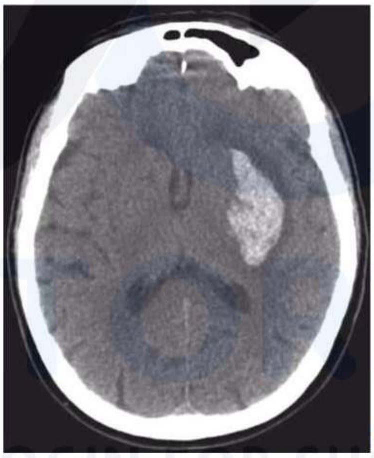

Fig: 1

- CT Brain axial view

↓

hyperdensity in L internal capsule

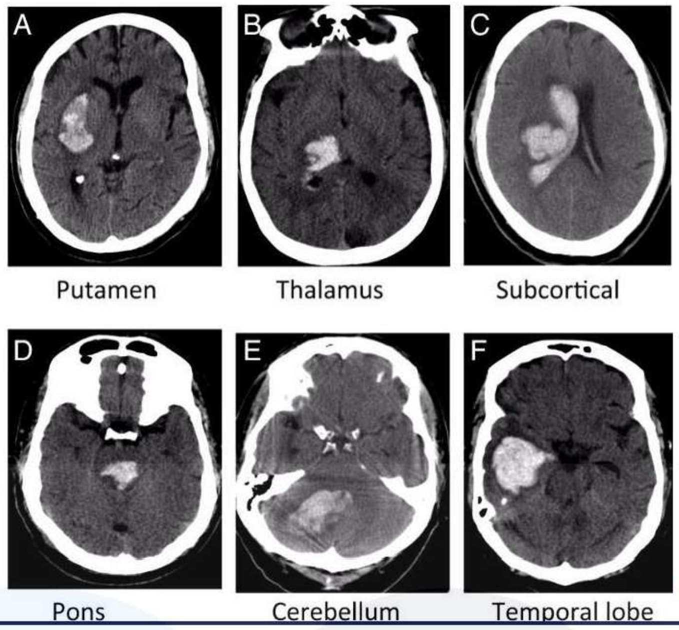

Fig: 2

Fig: 3

- Pontine bleed :

  Hyperpyrexia

  Hyperhidrosis

  Hyperpnea

  Pin point pupils

  quadriparesis

  Locked in syndrome

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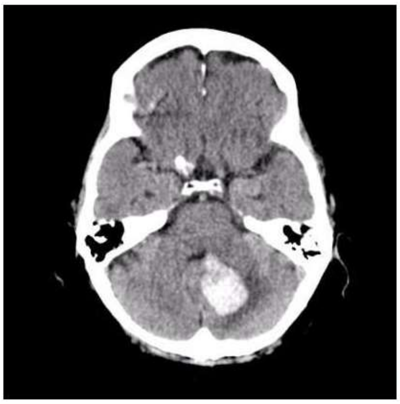

Fig: 4

- Bleed in cerebellum

↓

Chance of development of hydrocephalus

Bleed in infratentorial compartment more dangerous

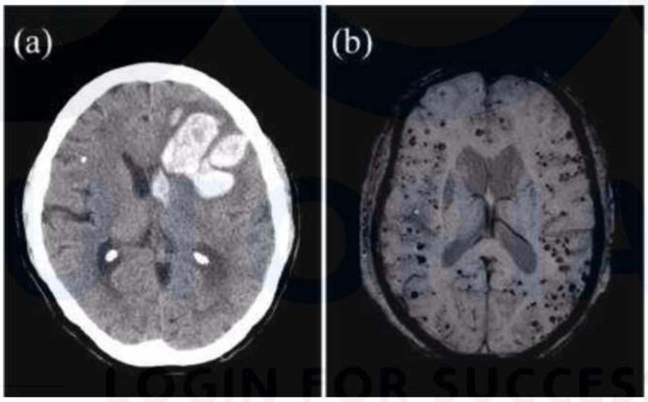

Fig: 5

- a. lobar bleed → frontal bleed
  b. susceptibility weighted imaging sequence (SWI) → MRI
  ↓
  micro bleeds

  (a, b) → cerebral amyloid angiopathy

- a. CT Brain with contrast → intracerebral bleed → active

↓

spot sign Q

- b. Plain CT

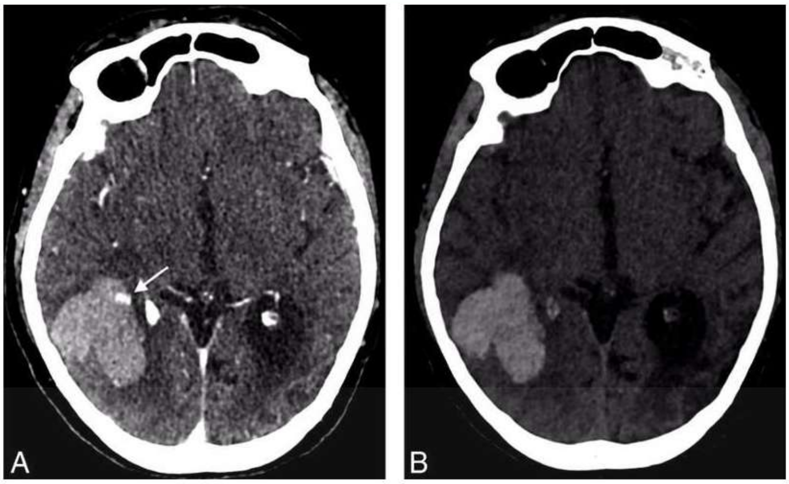

Fig: 6

Treatment 00:18:51

1.Vitals

ABC

2.Blood pressure control

Interact – 2 trials → systolic bp < 140mmhg [9]

3.Cerebral edema

- 30° propped up
- Hyperventilate
- Antiedema measures
- Target cerebral perfusion pressure (map – icp) → 50-70mmhg [9]

4.Coagulation parameters – abnormal

- Vitamin k antagonists
  - Prothrombin complex concentrates (pcc)
  - Vitamin k injection
  - Fresh frozen plasma
- Antidote for dabigatran – idaricizumab [9]

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- Antidote for factor x a inhibitors – andexanet alfa [9]

5.Surgical evacuation

ICH score 00:26:20

- Prognostication

The ICH Score	
CLINICAL OR IMAGING FACTOR	POINT SCORE
Age	
<80 years	0
> 80 years	1
Hematoma Volume	
<30 cc	0
>30 cc	1
Intraventricular Hemorrhage Present	
No	0
Yes	1
infratentorial origin of hemorrhage	
No	0
Yes	1
Glasgow Coma Scale Score	
13-15	0
5-12	1
3-4	2
Total Score	0-6 Sum of each category above

Subarachnoid haemorrhage 00:29:03

- Bleeding into subarachnoid space
- Etiology
  - Most common cause – trauma [9]
  - Rupture of berry/saccular aneurysms → most common non traumatic cause
  - Vascular malformations → av malformation
    Dural av fistula
  - Berry aneurysm – defect in tunica media
  - Majority of aneurysm – anterior circulation

↓

Most common site: junction of aca to acom

  - High chance of rupture in posterior circulation aneurysms
    - Top of basilar artery
    - Pcom
  - aneurysm > 7mm diameter, Aneurysm in basilar artery, Aneurysm in pcom artery – high risk of rupture
  - Giant aneurysm → diameter > 2.5 cm [9]

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Risk Factors for Subarachnoid Hemorrhage

- Modifiable Risk Factors
- Hypertension
- Smoking
- Heavy alcohol use
- Sympathomimetic drug use (eg, cocaine)

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Nonmodifiable Risk Factors

- Increasing age (peak in fifth and sixth decade)
- Female sex
- African American ethnicity
- Hispanic ethnicity
- Japanese or Finnish ethnicity
- Prior history of subarachnoid hemorrhage
- Family history of subarachnoid hemorrhage
- History of aneurysm in two or more first-gree relatives
- Autosomal dominant polycystic kidney disease
- Type IV Ehlers-Danlos syndrome
- Cerebral aneurysms of more than 7 mm in diameter
- Family history of subarachnoid hemorrhage
- History of aneurysm in tow or more first-degree relatives
- Autosomal dominant polycystic kidney disease
- Type IV Ehlers – Danlos syndrome
- Cerebral aneurysms of more than 7 mm in diameter

- Clinical features
  - Acute onset
  - Headache (thunderclap headache)
  - Focal neurological deficit
  - Increase icp (vomiting, double vision)
  - Abrupt loss of consciousness → coma and death
  - O/e: - neck stiffeners

Grading Scales for Subarachnoid Hemorrhage		
grade	HUNT-HESS SCALE	WORLD-FEDERATION OF NEUROSURGICAL SOCIETIES (WFNS) SCALE
1	Mild headache, normal mental status, no cranial nerve or motor findings	GCS score 15, no motor deficits
2	Severe headache, normal mental status, may have cranial nerve deficit	GCS score 13-14, no motor deficits
3	Somnolent, confused, may have cranial nerve or mild motor deficit	GCS score 13-14, with motor deficits
4	Stupor, moderate to severe motor deficit, may have intermittent reflex posturing	GCS score 7-12, with or without motor deficits
5	Coma, reflex posturing or flaccid	GCS score 3-6, with or without motor deficits

- Investigations
  - Ncct → blood in subarachnoid space
    Diffuse sah → hyper densities in subarachnoid space

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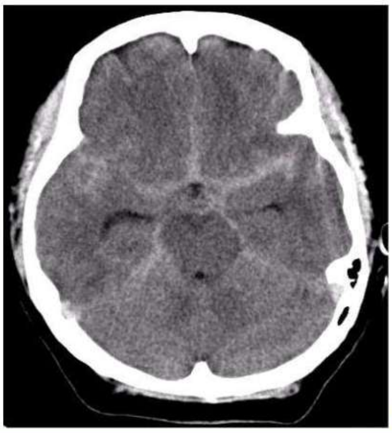

Fig: 7

- Ncct – negative (10-15% of cases)

↓

Lumbar puncture → blood in csf

xanthochromia in csf

Traumatic lp vs sah lumbar puncture

↓↓

Collect csf in 4 bottles

↓

- Traumatic → first bottle red and subsequent bottles will fade in color
- SAH → all 4 bottles red in color

- CTA
- MRA

} to visualize vessels and look for aneurysm

- DSA (Digital subtraction angiography)

↓

IOC for diagnosing aneurysm

- Complications
  - Rupture
  - Delayed cerebral ischemia (4-14 days of bleed)
    - Most common cause of late morbidity and mortality in sah

- Hydrocephalus
- Hyponatremia either due to
  - Cerebral salt wasting syndrome (or)
  - SIADH

- Management

1.Vitals,

2.ABC

3.Glucocorticoids → some relief in headache and neck stiffness

4.Target cpp: - 60-70mmhg [9]

5.Target systolic bp < 160 mmhg [9]

6.Triple h therapy

- htn
- Hemodilution
- Hypervolemia

(htn, Hemodilution, Hypervolemia) – to avoid delayed cerebral ischemia

  - Euvolemia (according to ASA)

7.Cerebroselective CCD

- Nimodipine
  - Vessel dilatation
  - 30mg every 4 hourly

8.Prophylactic antiepileptics in immediate post haemorrhagic period

9.Surgical treatment

- Clipping → open procedure
- Coiling → endovascular procedure

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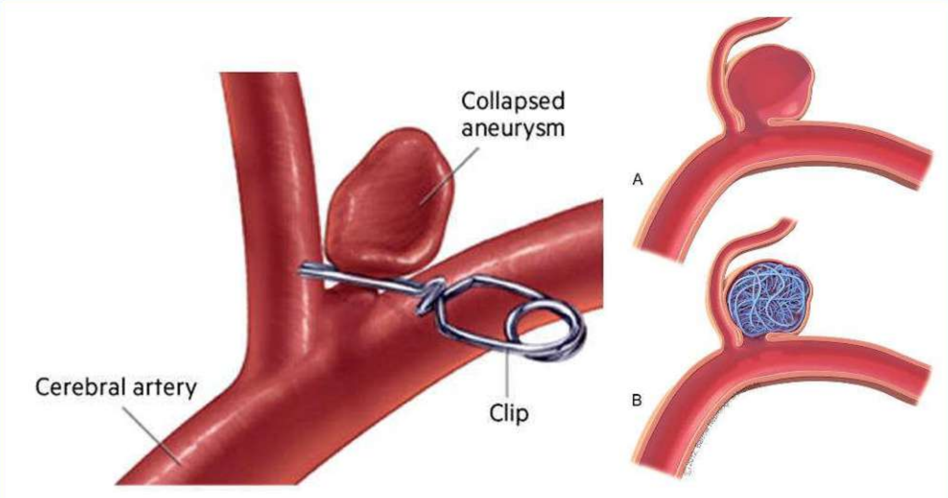

Fig: 8

According to ASA, coiling > clipping.

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POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

Introduction 00:00:35

- Hyper perfusion syndrome
- Occurs in setting of accelerated HTN
- Because cerebral autoregulation disruption
- Sympathetic – less abundant in posterior aspect
- Hyper perfusion damage
- Also occurs due to hypoperfusion and endothelial dysfunction
- Occurs in sepsis.

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Pre – disposing factors 00:04:10

- Hypertensive crisis
- CKD
- Sepsis
- Eclampsia
- Seizure
- Sympathomimetic drugs
- Cyclosporine
- Tacrolimus
- Head injury

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Clinical features 00:05:58

- Headache
- Seizures
- Encephalopathy
- Visual disturbances
- Other focal neurological deficits

Diagnosis 00:07:00

- MRI → T2 flair axial sequence

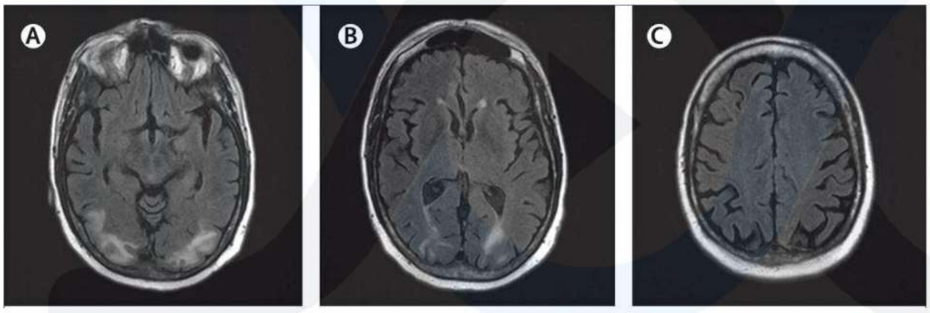

Fig: 1

- Hyperintensity in parieto-occipital region
- Diffusion restriction & contract enhancement are absent in PRES (15% cases)

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Prognosis:

- Good if treated early

Treatment 00:09:18

- Optimum BP control
- 25% reduction in BP
- Seizures – Antiepileptics
- Antiedema measures.

CEREBRAL VENOUS THROMBOSIS

Venous stroke 00:00:24

- Arterial Stroke > Venous Stroke
  - Venous Stroke
    a. Venous system: Superficial venous system
    b. Deep venous system
    c. Dural venous sinuses
    (a–c: valveless)

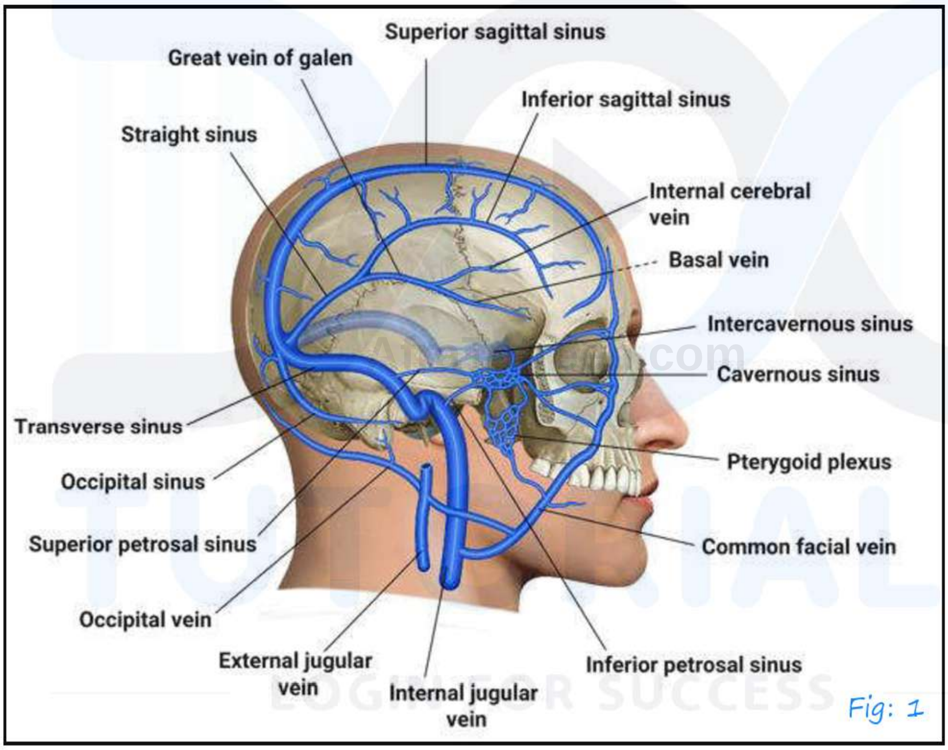

Fig: 1

Pathophysiology: 00:03:00

- Pathophysiology:
  - Venous thrombosis → ischemia and infraction
    → Venous HTN
    ↑ ICT

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Clinical features 00:03:52

- Clinical features: Headache
  - Seizures
  - Increases ICT (vomiting, diplopia)
  - Focal neurological deficit
  - Encephalopathy

    ↓

    Coma & death
- More common in females

Predisposing factors 00:04:58

- Predisposing factors: Pregnancy
  - Puerperium
  - Use of OCP's
  - Obesity
  - Hypercoagulable:
    - a. Procoagulant condition
    - b. Factor V Leiden mutation
    - c. Protein C deficiency
    - d. Protein S deficiency
    - e. Antithrombin 3 deficiency
  - Malignancies
  - Dehydration
  - Infection (meningitis, ASOM)

Diagnosis 00:07:10

- Diagnosis: MRI Brian + MR Venogram

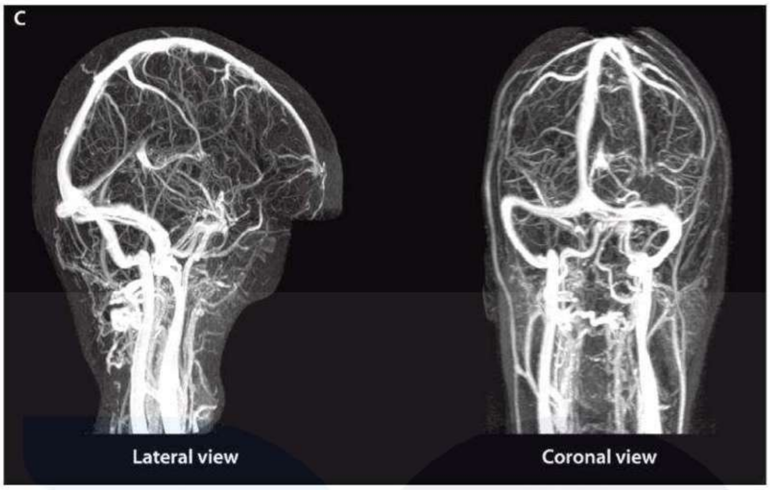

Fig: 2

- Question: Most common sinus involved in thrombosis
  – Superior sagittal sinus

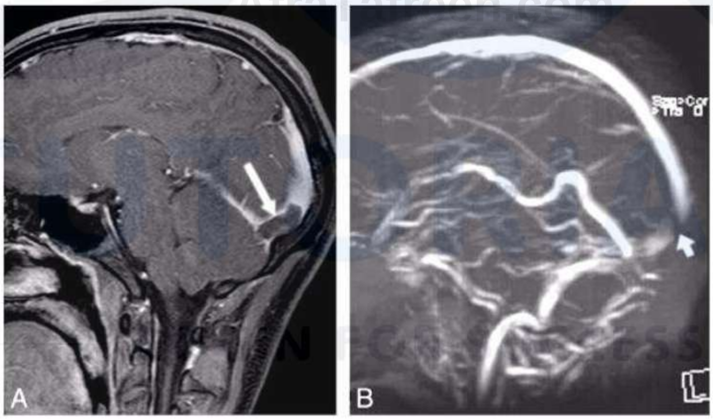

Fig: 3

→ MRI sagittal T_1 contrast sequence
MR Venogram

- CT Brain: Dense card sign
  Dense Clot sign
- CT/MRI contrast: Empty delta sign

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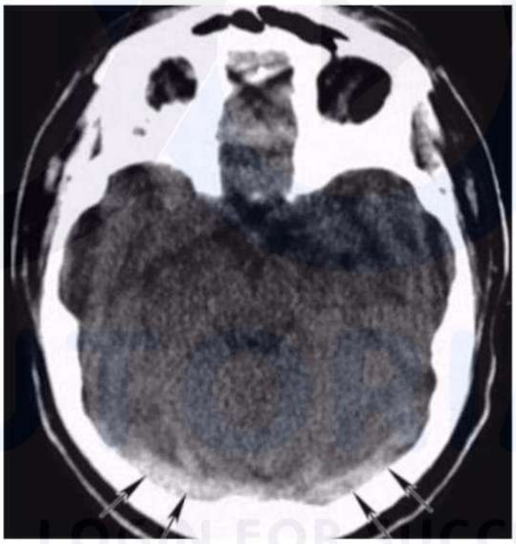
Fig: 4

→ Plain CT Axial

↓

Dense Clot sign



Dense Cord sign Fig: 5

Contrast CT → Empty delta sign Fig: 6

Treatment 00:14:22

- Treatment: Anticoagulation

  a. Unprovoked → Duration: 6-12 months

  Target INR: 2-3

  b. Provoked → Duration: 3-6 months

  Target INR: 2-3

  c. Severe thromboOphilia → Lifelong anticoagulation

  Target INR: 2-3

- Seizures: Antiepileptics
- Raised ICT: Antioedema measures.

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INTRODUCTION AND CLASSIFICATION OF HEADACHE

Pain sensitive structure 00:02:44

- Scalp
- Falx cerebri
- Dural venous sinuses
- Vessels of circle of Willis
- Proximal segments of large pial arteries

Pain insensitive structure 00:03:56

- Most of brain parenchyma
- Pial veins
- Choroid plexus
- Ventricular ependyma

Key areas in pain perception 00:05:32

1. Dura and large meningeal vessels → Trigeminovascular system
2. Periaqueductal gray matter, Locus ceruleus, Raphe nuclei, Rostral ventromedial medulla } Brain stem
3. Trigeminal nucleus → trigeminocervical complex
4. Ventroposteromedial thalamus
5. Cortex
6. Hypothalamus.

Classification 00:09:20

1. Primary headache
   - Headache and associated features
   - Includes: -
     - Tension type headache (Most common type)
     - Migraine
     - Trigeminal autonomic cephalgias
     - Others
2. Secondary headache
   - Exogenous cause
   - Includes: -
     - Infections
     - Vascular
     - Brain tumor
3. Pain full cranial neuropathies
   - Trigeminal neuralgia

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Common Causes of Headache

Primary Headache		Secondary Headache	
Type	%	Type	%
Tension-type	69	Systemic infection	63
Migraine	16	Head injury	4
Idiopathic stabbing	2	Vascular disorders	1
Exertional	1	Subarachnoid hemorrhage	<1
Cluster	0.1	Brain tumor	0.1

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Red Flag Signs

- Headache symptoms that suggest a serious underlying disorder
  - Sudden – onset headache
  - First severe headache
  - "worst" headache ever
  - Vomiting that precedes headache
  - Subacute worsening over days or weeks
  - Pain induced by bending, lifting, cough
  - Pain that disturbs sleep or presents immediately upon awakening
  - Known systemic illness
  - Onset after age 5
  - Fever or unexplained systemic signs
  - Abnormal neurologic examination
  - Pain associated with local tenderness, e.g., region of temporal artery

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TENSION TYPE HEADACHE

- Common in middle aged females
- Clinical features – Bilateral band like sensation (tightness)
- Also referred to featureless headache
  ↓
  No photophobia, Phonophobia, osmophobia
- Mild-moderate
- Waxing and waning
- Hours- days

Features 00:01:12

- Emotional tension
- Muscle tension
- Emotional tension → Muscle tension
- Central pain modulation
- Low pain threshold
- Also referred to as muscle contraction headache
- 2types
  - Episodic
  - Chronic → Last > 15days a month

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Treatment 00:06:02

- Acute – Aspirin, Acetaminophen, NSAIDS
- Prophylaxis: Amitriptyline.

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MIGRAINE

Migraine 00:00:30

- 2nd most common type of primary headache
- F>M

Clinical features 00:01:53

- Episodic headache
- Nausea
- Vomiting
- Photophobia
- Phonophobia
- Osmophobia

symptoms accompanying severe migraine attacks in 500 patients	
symptom	patients affected. %
Nausea	87
Photophobia	82
Lightheadedness	72
Scalp tenderness	65
Vomiting	56
Visual disturbances	36
Paraesthesia	33
Vertigo	33
Photopsia	26
Alteration of consciousness	18
Diarrhea	16
Fortification spectra	10
Syncope	10
Seizure	4
Confusional state	4

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Diagnosis criteria 00:04:08

- Clinical criteria by international headache society (IHS)

At least 2 of the following features	Plus at least 1 of the following features
Unilateral pain Throbbing pain Aggravation by movement Moderate or severe intensity	Nausea/Vomiting Photophobia and phonophobia

Phases 00:07:36

- Premonitory phase
  - 1-2hours or day before episode
  - Yawning
  - Thirst
  - Polyuria
  - Diarrhoea
  - Fatigue
  - Depression
- Aura phase
  - 20-25% of migraine patients
- Visual aura – Zig Zag lines
  - Flashing lights
  - Fortification spectra
- Sensory- parasthesias, numbness
- Auditory

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- Headache phase
- Post drome phase
  - Fatigue
  - Depression

Migraine triggers 00:11:58

- Increased sensory sensitivity
- Common triggers
  - Glare/Bright light
  - Hungers
  - Stress
  - Alcohol
  - Menstrual hormonal disturbances
  - Odours
  - Sleep deprivation/excess sleep
  - Nitrates

Classification 00:14:04

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- Migraine with aura (Classical migraine)
- Migraine without aura (Common migraine)
- Chronic migraine
  - >15days month
  - ≥ 8days – well established migraine attack
- Complicated migraine
  - Status migranosus → 72hours of headache migraine with infarction

- Probable migraine
- Episodic syndrome also known as migraine
  - BPPV
  - Cyclical vomiting syndrome

Migraine with aura

- Typical aura with headache
- Typical aura without headache (Acephalgic migraine)
- Migraine with brainstem aura
  - ≥ 2 brain stem features like ataxia, diplopia, vertigo
  - Previously referred to as basilar migraine
- Hemiplegic migraine
  - Sporadic
  - Familial

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Pathophysiology 00:22:51

- Combination of Genetic factors
  Host
  Environments factors

Genetic factors

- Episodic migraine – No single gene with definite association
- Familial hemiplegic migraine – Genetics better defined

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2 theories

Vascular theory | Neurogenic theory

Vascular theory ↓

- Vascular headache
- Aura phase occurs because of vasoconstriction
- Headache phase because of vasodilation

Neurogenic theory

- Brain disorder with 2° vascular effects
- In aura phase → Initially vasodilation p/b vasoconstriction
- Problem of maladaptive brain
- Increased sensory sensitivity
- Neurogenic inflammation

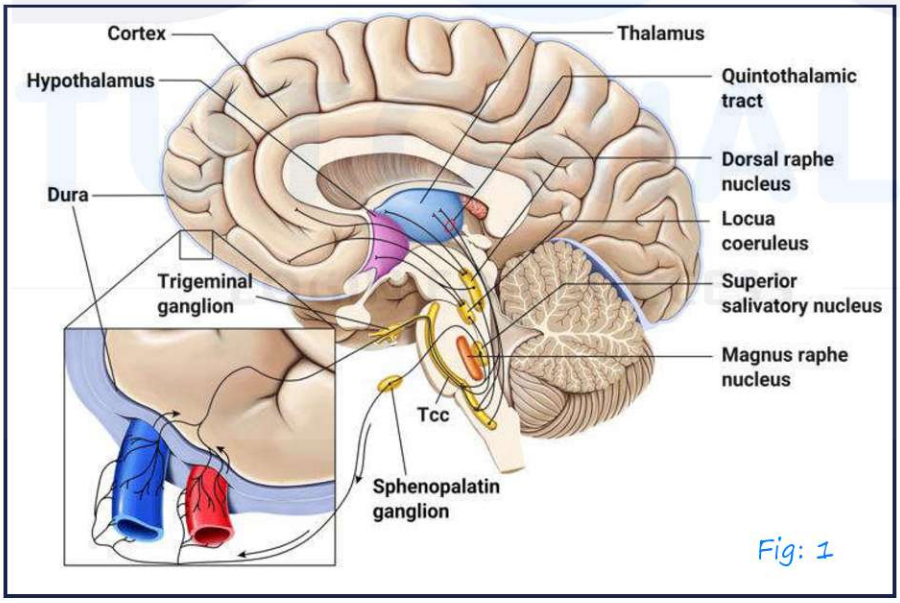

Fig: 1

- Trigeminal nerve endings in meningeal vessels are pain insensitive

Key points

1.Migraine generator

- Hypothalamus
- Brainstem
- Hypothalamo-Brainstem axis
- Hypothalamo – Pontine axis
- Premonitory symptoms are due to hypothalamus

2.Aura

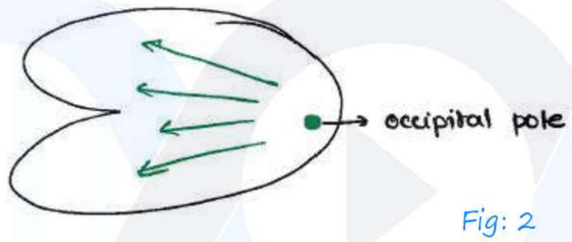

Fig: 2

- Aura occurs due to disruption of certain ionic gradients in cortex (Occipital cortex)
- From occipital pole some depolarisation waves are spreading at role of 2-4mm/min
- Wave of depolarisation is referred to as cortical spreading depression/depolarisation
- This causes aura
- Cortical spreading depression in electrophysiological equivalent of aura
- Depolarization → Positive visual phenomenon
- Repolarization → Negative visual phenomenon

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3.Headache phase

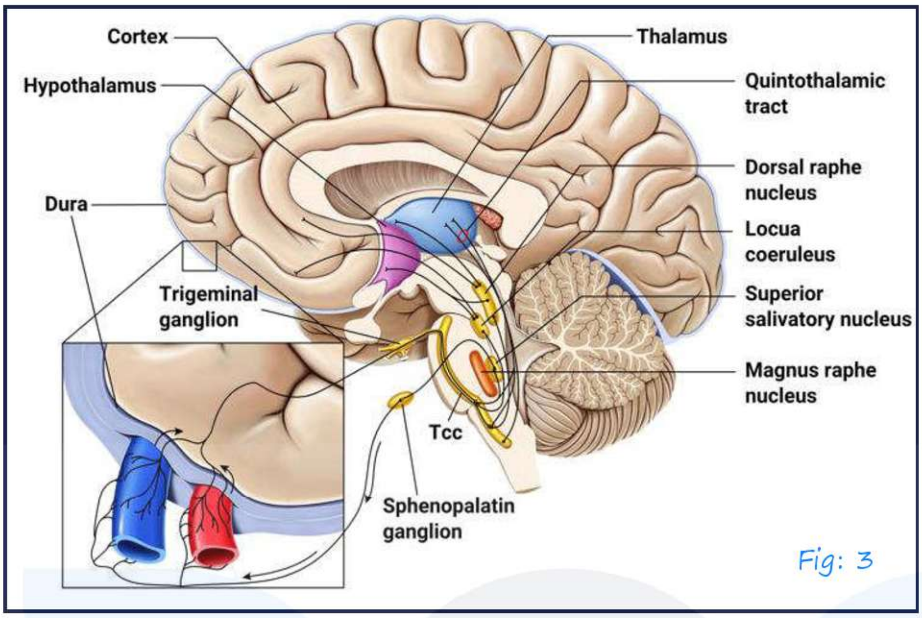

Fig: 3

- Trigeminal nucleus extending up to C2 level
- Trigemino cervical complex consists (TCC) of
- Trigeminal nucleus
- Trigeminal ganglion
- Trigeminal nerve divisions
- In headache phase activation of TCC
- Release of neurotransmitters
- CGRP (Calculation Gene related peptide)
- VIP (Vasoactive intestinal peptide)
- Serotonin
- TRPV1
- TRPA1
- Nitric oxide
- Neurogenic inflammation
- Plasma protein leakage

- Afferent impulses coming from V1 division of trigeminal nerve → brain stem
- If informs the key structures
- Locus coeruleus
- Raphe magnus nucleus
- Rostral ventro medial medulla
- Periaqueductal Gray matter (PAG)

Familial hemiplegic migraine 00:47:06

3 types

FHM type 1
↓
- 50% cases
- Ca^{2+} channel dysfunction
- Gene affected – CACNA1A

FHM type 2
↓
- ATP channel
- Na^{+} – K^{+} ATPase
- ATPIA2

FHM type 3
↓
- Na^{+} channel
- SCNIA

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Familial hemiplegic migraine 00:47:06

- MIDAS – Migraine disability assessment scale questionnaire

MIDAS Questionnaire

- INSTRUCTIONS: Please answer the following questions about ALL headaches you have had over the last 3 months. Write zero if you did not do the activity in the last 3 months.

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1.On how many days in the last 3 months did you miss work or school because of your headaches?..days

2.How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches (do not include days you counted in question 1 where you missed work or school)?.._days

3.On how many days in the last 3 months did you not do household work because of your headaches? .... days

4.How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches (do not include days you counted in question 3 where you did not do household work)?..days

5.On how many days in the last 3 months did you miss family, social, or leisure activities because of your headaches?..............days

A.On how many days in the last 3 months did you have a headache? (If a headache lasted more than one day, count each day) ....days

B.On a scale of 0-10, on average how painful were these headaches? (Where 0 = no pain at

all, and 10 = pain as bad as it can be.)

....days

- Migraine Disability Assessment Score
- (Questions 1-5 are used to calculate the MIDAS score.)
- Grade I-Minimal or Infrequent Disability: 0-5
- Grade II-Mild or Infrequent Disability: 6-10
- Grade III-Moderate Disability: 11-20
- Grade IV-Severe Disability: > 20

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Acute treatment

- Mild moderate → Oral
- Moderate severe → Parenteral

Drugs

- Acetaminophen
- NSAIDS
- 5HT 1B/1D agonists
- Dopamine antagonist
- CGRP receptors antagonist (Gepants)
- 5HT 1F agonists

Neuromodulation device

↓

- Transcranial magnetic stimulation device (TMS)
- Non-invasive vagal nerve stimulation

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Mild moderate attack

- Acetaminophen
- Aspirin
- NSAIDS
- Naproxen 250mg BD → 500mg BD
- Ibuprofen
- Diclofenac
- Tolfenamic acid

Dopamine antagonist

- Anti-Migraine effects prokinetic agents
- Metoclopramide
- Prochlorperazine
- Chlorpromazine

Moderate severe

- Triptans
- 5HT 1B/1D against

Selective → Triptans
Non - Selective → Ergots

Triptans:

- Sumatriptan
- Atrotriptan
- Electriptan
- Zohn triptan
- Naratriptan
- Frovatriptan

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- Triptans have difference in clinical efficacy
- Preparations → Oral

  → SC → Sumatriptan → 6mg SC

  → Nasal spray → Sumatriptan, zolmitriptan
- Problems – Not useful in
  - Migraine with aura
  - Hemiplegic migraine
  - Migraine in pregnancy
  - Cerebrovascular disease
  - Coronary artery disease
  - Uncontrolled HTN
- Recurrence of headache associated with triptans

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Ergot

- Ergotamine
- Dihydroergotamine → SC/i.m/i.v → 1mg
- Increased chance of nausea
- Level B evidence except dihydroergotamine → Level A evidence
- 5HT 1B/1D → Predominant action on blood vessels
- 5HTIF agonist → Lasmiditan → Action on neural targets

↓

Named as NAAMA

↓

Neurally acting antimigraine agents

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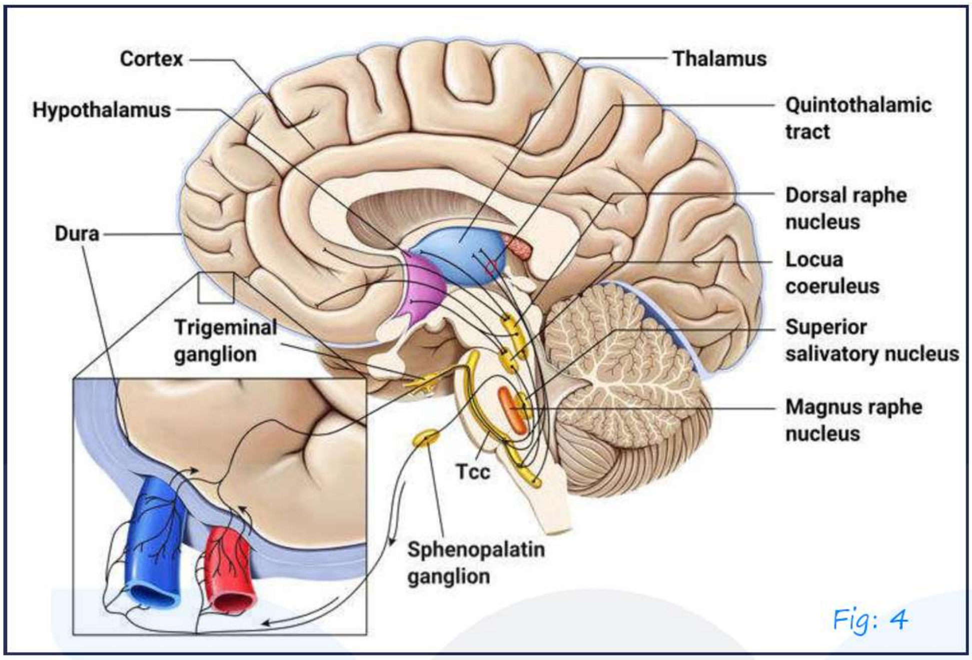

Fig: 4

- CGRP – Calcitonin gene related peptide
- Gepants – Antagonists to CGRP receptors
  - Ubrogepant
  - Rimegepant
- Monoclonal antibody targeting CGRP receptor → Erenumab
- Target CGRP – Eptinezumab
  - Galcanezumab
  - Framenezumab

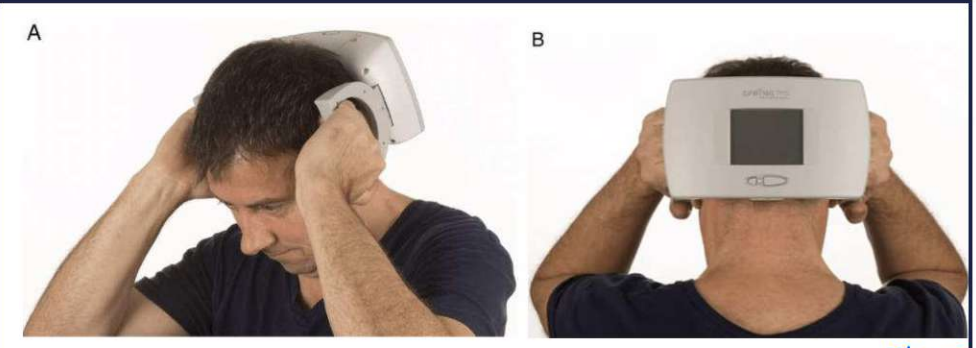

Fig: 5

- Transcranial magnetic stimulation device

  ↓

  Targets cortical spreading depression

Fig: 6

- Vagal nerve stimulation device

  ↓

  Stimulate (L) vagus

- Pregnant female – Acute migraine episode

  ↓

  NSAID's

  Steroids

  Dopamine antagonist

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Prophylaxis 01:16:53

- No. of episodes ≥ 1 week
- Agents:

  1.Beta blockers – Propranolol (C/I in asthma)

  - Anti-depressants
  - Nortryptilline

  2.Antidepressants

  - Amitryptilline

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- Nortryptilline

3.Anticonvulsants

- Topiramate
- Valproate

4.Calcium channel blockers

- Flumarazine

5.Serotonergic drugs – Pizotifen

6.TMS

7.Chronic migraine

- Ona botulinum toxin

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TRIGEMINAL AUTONOMIC CEPHALGIAS (TAC'S)

Introduction 00:00:40

- Cluster headache
- Paroxysmal hemicrania
- SUNCT/SUNA
- Hemicrania continua
- Group of disorders with headache associated with prominent cranial autonomic symptoms
  - Conjunctival injection
  - Lacrimation
  - Nasal fullness
  - Rhinorrhea
  - Aural fullness

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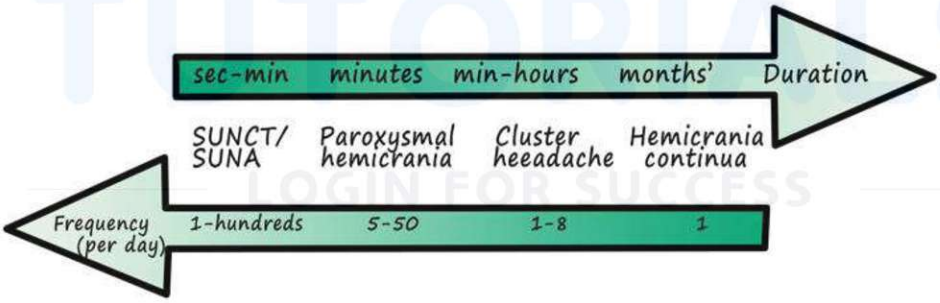

Cluster headache 00:05:00

- Most common TAC
- Age: - 3rd decade
- M > f (3:1 ratio)
- Characteristics: -
  - Unilateral pain

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- Retroorbital and temporal
- Very severe pain
- Called suicide headache
- Lasts for 15-180 minutes
- Alcohol – trigger
- Prominent cranial autonomic symptoms
- Migraneous features
- Nausea
- Vomiting
- Photophobia → U/L
- Phonophobia
- Restless
- Periodicity
- Episodic (80%)
- Chronic (20%)

- Episodic: -
  - Episodes occur in clusters /bouts
  - 8-10 weeks recurrent bouts
  - Episodes – 1/day → 8 /day
  - Periodicity
  - Remission → 1 year
- Chronic: - duration of remission < 3months
  - Pathogenesis
- Key area – Hypothalamus (posterior)
- Others – superior salivatory nucleus (pons)
  Trigeminal nucleus

- Periodicity is present in cluster headache due to involvement of hypothalamus
  - Treatment and prophylaxis
- Acute treatment: fast acting

1. Oxygen (Doc)
   Hight flow O_2
   100% O_2
   10-12 L/min for 20 minutes

   } non rebreathing mask

   ↓

   Increase 15L/minutes
2. Triptan
   - Subcutaneous sumatriptan
   - Nasal spray – sumatriptan and zolmitriptan
   - Oral sumatriptan – not preferred
3. Noninvasive vagal nerve stimulation

Prophylaxis

Short term	Long term
↓	↓
• Steroids ↓ Prednisone (21 days)	• Verapamil → preferred
• Verapamil	• Topiramate
• Greater occipital nerve injection	• Lithium
	• Melatonin
	• Gabapentin

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- Neuromodulation
  - Non – invasive vagal nerve stimulation (nVNS)
  - Sphenopalatine ganglion stimulation

Paroxysmal hemicrania 00:24:16

- F = M [Q]
- U/L Headache in retro-orbital region
- Associated with cranial autonomic symptoms
- Duration: - 2-30 minutes [Q]
- > 5 episodes/day
- Treatment
  - Prophylaxis
- Indomethacin
- nVNS
- topiramate
- piroxicam

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SUNCT / SUNA 00:28:48

- SUNCT – Short lasting unilateral neuralgiform headache with conjunctival injection and tearing
- SUNA – short lasting unilateral neuralgiform headache with cranial autonomic symptoms
- SUNCT – Both conjunctiva injection + tearing
- SUNA – either conjunctival injection/tearing/nil
- Duration: 5-240 seconds [Q]
- 100 of episodes can occur per day

- F = M
- Treatment: -
  - Admission → acute → I.V Lignocaine
  - Prophylaxis → lamotrigine
    Topiramate
    Gabapentin

Hemicrania continua 00:32:52

- Age: - 10-70 years
- F > M
- Autonomic symptoms present
- Prophylaxis: - indomethacin – 25mg TID → 75mg TID
- nVNS
- any TAC → do MRI to rule out 2° TAC.

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CDH AND NDPH

CDH 00:00:58

- Chronic daily headache (CDH)
  - > 15 days/month

Classification of Daily or Near-Daily Headache		
Primary		
>4 H DAILY	<4 H DAILY	SECONDARY
Chronic migraine [a]	Chronic cluster headache [a]	Posttraumatic Head injury Iatrogenic Postinfectious
Chronic tension-type headache [a]	Chronic paroxysmal hemicrania	Inflammatory, such as Giant cell arteritis Sarcoidosis Behçet's syndrome
Hemicrania continua [a] New daily persistent headache	SUNCT/SUNA Hypnic headache	Chronic CNS infection Medication-overuse headache

DOT TUTORIALS LOGIN FOR SUCCESS

Medication overuse headache

- Opioids
- Combination analgesics
- Triptans

NDPH 00:05:52

New daily persistent headache (NDPH)

- Onset of headache daily at a particular time and persistent throughout the day.

Differential Diagnosis of New Daily Persistent Headache	
PRIMARY	SECONDARY
• Migrainous-type • Featureless (tension-type)	• Subarachnoid hemorrhage • Low cerebrospinal fluid (CSF) volume headache • Raised CSF pressure headache • Posttraumatic headachea • Chronic meningitis

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SECONDARY HEADACHES

Secondary headaches 00:00:30

- Infections
- Vascular (AV malformations CVT)
- Tumors
- Low CSF pressure
- High CSF pressure

Low CSF pressure headache 00:01:55

- Also called Low CSF volume headache
- Post lumbar puncture headache
- Spontaneous intracranial hypotension (SIH)
  - Predisposing factors
- Connective tissue disorder
  - Marfan's syndrome
  - Ehler danlos syndrome
- ADPKD
  - Clinical features
- Positional headache
  - Increased on sitting and standing
  - Decreased on supine
  - Investigations
- LP: - opening pressure < 60mm H_2O
- MRI brain with contrast
  - Pachymeningeal enhancement → Egg shell like

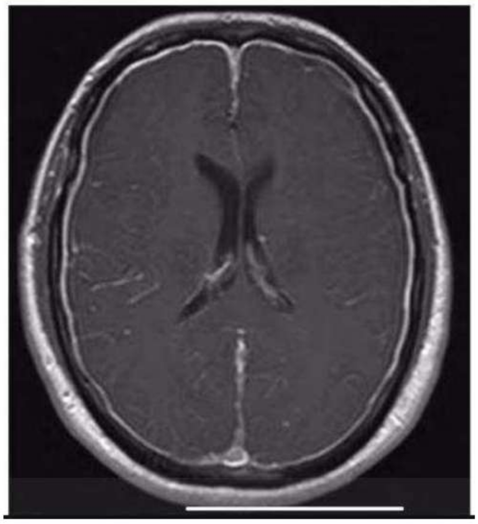

Fig: 1

- Pachymeningeal
- Eiffel tower sign
- Subdural effusions

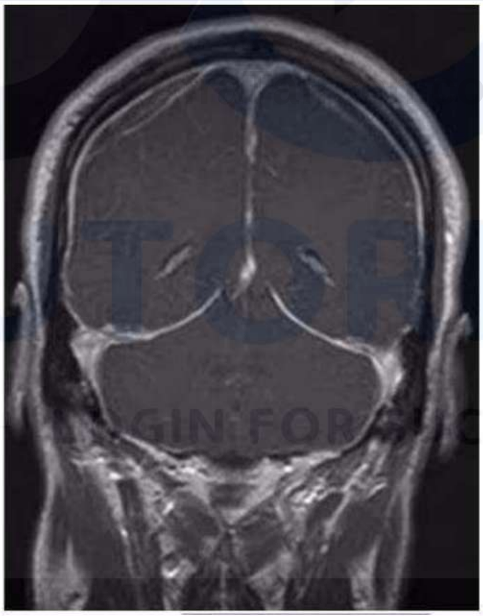

Fig: 2

- Cerebellar tonsillar descent

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Fig: 3

- Ant. Aspect of pons flattened
- Crowded posterior fossa
- Sagging of brain

- MRI Myelography/CT myelography → To demonstrate the leak
  - Treatment
- Hydration
- Bed rest
- Raise foot end of the bed
- Caffeine, theophylline
- Abdominal binders
- Analgesics
- Steroids
- B/L Greater occipital nerve stimulation
- Epidural blood patch [Q] – 10-20ml of patient's blood Injected into epidural space

Idiopathic intracranial hypertension 00:16:44

- Also known as pseudotumor cerebri
- Obese middle-aged females
- Predisposing factors
  - Drugs
  - Addison's disease, Cushing's syndrome
  - Anemia
  - Renal failure
  - SLE, sjoggrens syndrome
- Pathogenesis of IIH
  - Reduced CSF absorption – arachnoid villi
  - Transverse venous sinus stenosis
  - Increased CSF production at choroid plexus
- Clinical features:
  - Features of raised ICT
    1. Headache
    2. Blurring of vision
    3. Diplopia (B/L 6th nerve palsy)
    4. Pulsatile tinnitus
  - Examination findings
    1. Papilledema
    2. ± B/L lateral rectus palsy
    3. Rest of neurological examination normal
- Investigations
  - CSF: - increase opening pressure
    Test of CSF analysis normal

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- Imaging: - MRI brain with contrast + MR venogram (MRV)

D/W: - cerebral venous sinus thrombosis

A.Empty sella sign

B.Enlarged optic nerve sheath diameter

C.Transverse venous sinus stenosis

D.Flattening of posterior aspect of eyeball / globe

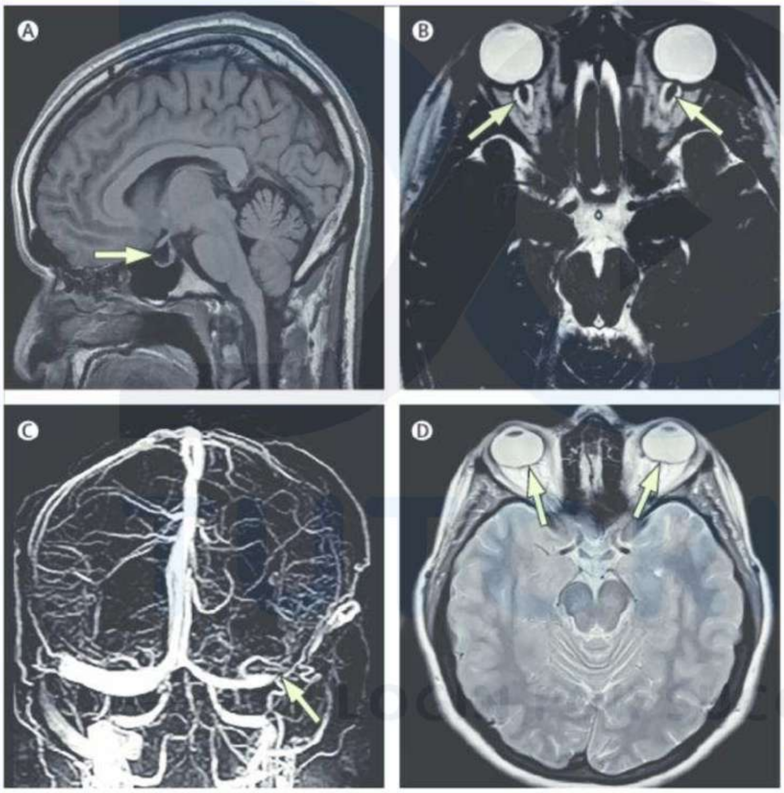

Fig: 4

- Modified dandy criteria
  - Consists of

    1.Papilledema

    2.Normal neurological examination exception of B/L 6th nerve

3.Imaging will no show any mars lesions, hydrocephalus

4.Normal CSF composition

5.Raised CSF pressures

- > 250 mm CSF for adults
- > 280 mm CSF for children

- Treatment

1.Lifestyle modification

- Weight reduction (low calorie, low salt diet, exercise regimens)

2.Medical therapy

- Acetazolamide
- Topiramate (weight loss)
- Fulminant IIH: - loss of visual activity within 4 weeks

↓

Steroids

3.Surgical treatment

- Optic nerve sheath fenestration
  - Severe deterioration of visual acuity
- VP shunting – features of raised ICT prominent
- Transverse venous sinus shunting

Thunderclap headache 00:38:03

- Explosive onset
- Reaches maximum intensity in 60 seconds

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- Worst headache
- Visual analog scale > 7
- Etiology
  - Subarachnoid hemorrhage
  - 3rd ventricular colloid cyst
  - Pituitary apoplexy
  - Cerebral venous sinus thrombosis
  - Intraventricular hemorrhage
  - Acute subdural hematoma
  - Intracerebral hematoma
  - Reversible cerebral vasoconstriction syndrome (RCVS)
- Post-partum angiopathy
- Vasoactive substances and drugs
- Characterized by multifocal vasospasm.

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BASAL GANGLIA PHYSIOLOGY

Movement disorders 00:00:30

Hypokinetic | hyperkinetic

- Tremors
- Tics
- Dystonia

(Tremors, Tics, Dystonia) – basal ganglia dysfunction is implied, but not proven

- Restless leg syndrome
- Hemifacial spasm
- Stiff person syndrome
- Essential tremor

(Restless leg syndrome, Hemifacial spasm, Stiff person syndrome, Essential tremor) – Dysfunction outside basal ganglia

Functions of basal ganglia 00:03:45

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1. Fine tuning of motor activities
2. Regulation of tone
3. Role in reward, cognition, motivation, emotion

- Basal ganglia – important component of extrapyramidal system
  - Dr. Samuel Alexander Wilson

↓

Introduction the terminology extrapyramidal system

Fig: 1

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Anatomy of basal ganglia 00:06:02

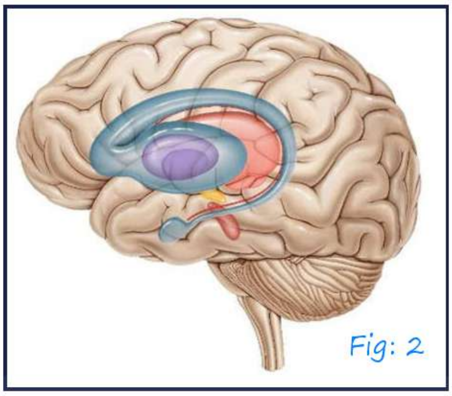

Fig: 2

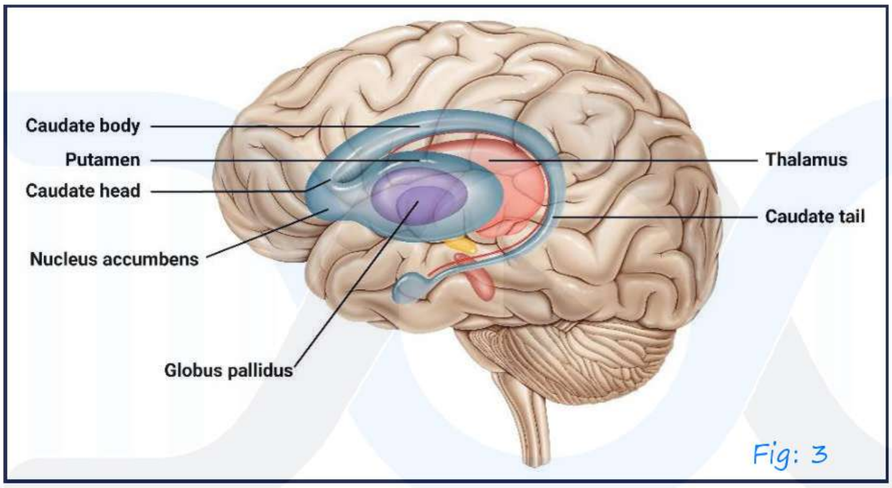

Fig: 3

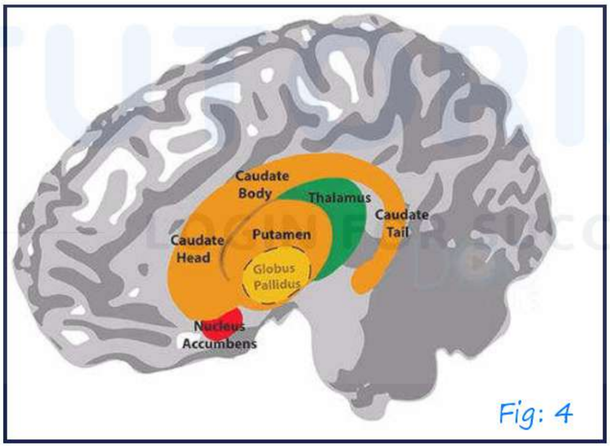

Fig: 4

- Caudate tail terminates in amygdaloid body
- Basal ganglia is comprised of
  - Caudate nucleus
  - Putamen
  - Globus pallidus

- Interna
- Externa

– Subthalamic nucleus

– Substantia nigra

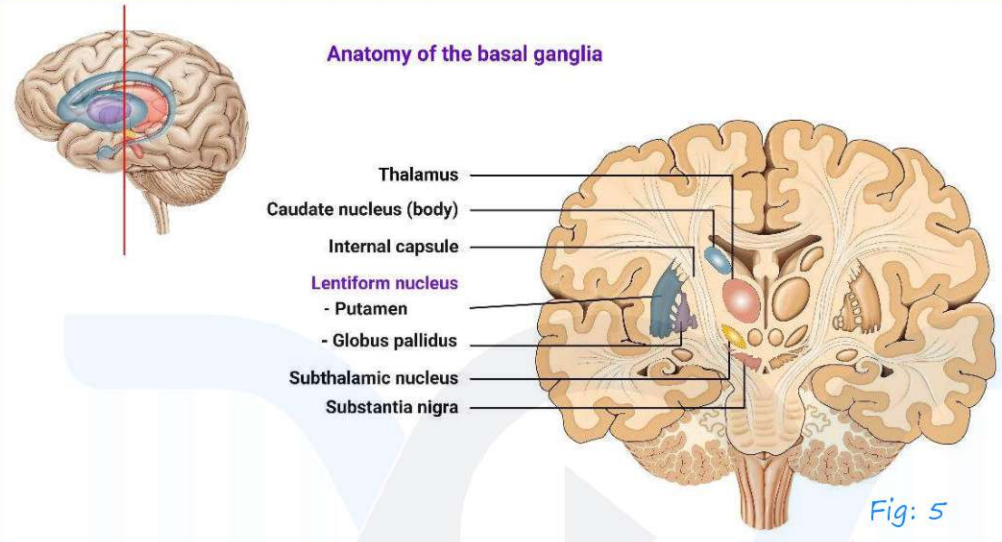

Fig: 5

- Caudate nucleus + putamen → striatum
- Putamen + globus pallidus → lentiform nucleus
- Caudate + lentiform nucleus → corpus striatum

Basal ganglia interconnections 00:10:16

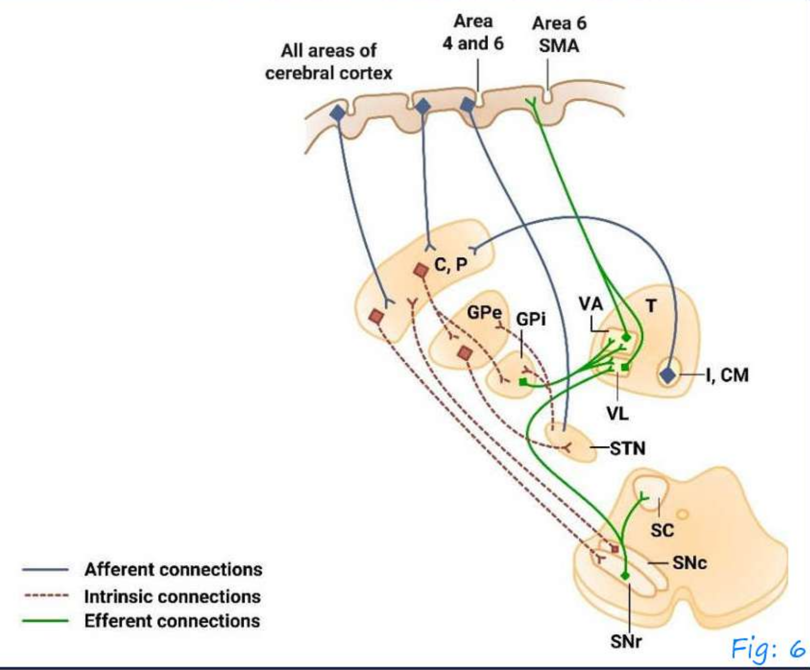

Fig: 6

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- Striatum – afferent
- Globus pallidus – efferent

Pharmacology of Basal ganglia 00:11:40

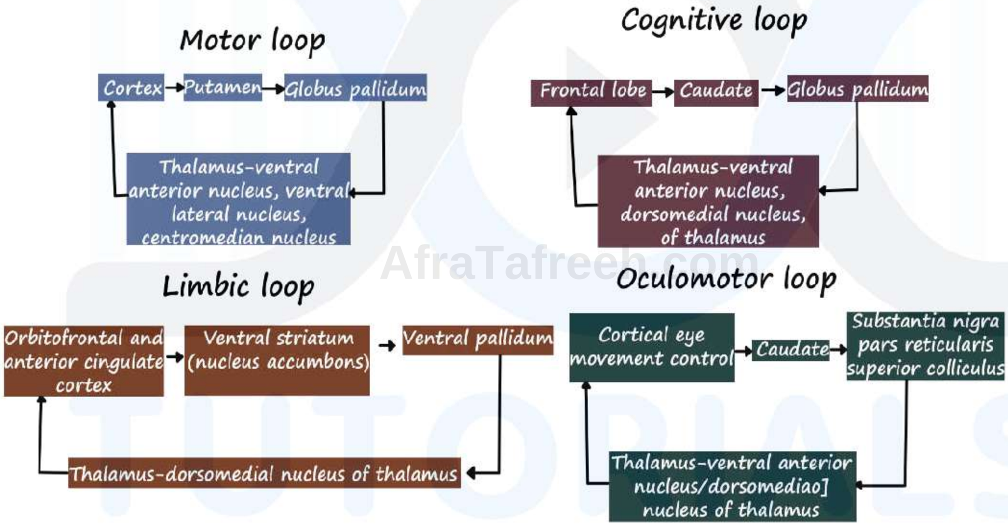
Pharmacology of the Basal Ganglia	
Pathway	Transmitter
STRIATAL AFFERENTS	
Cerebral cortex→ striatum	
Cerebral cortex → STN	Glutamate
Locus coeruleus → striatum	Norepinephrine
Locus coeruleus → SN	Norepinephrine
Raphe nuclei → striatum	Serotonin
Raphe nuclei → SN	Serotonin
Thalamus → striatum	Acetylcholine?
SNC striatum	Glutamate? Dopamine, cholecystokinin
INTRINSIC CONNECTIONS	
Striatal interneurons	GABA, acetylcholine
Striatum → GPi	Somatostatin, neuropeptide Y
Striatum → SNr	Nitric acid, calretinin
Striatum → GPe	GABA, substance P
GPe- STN	GABA, dynorphin, substance P
STN GPI, SNr, GPe	GABA, enkephalin, glutamate
STRIATAL EFFERENTS	
GPI→ thalamus	GABA
SN thalamus	GABA

- Excitatory and inhibitory neurotransmitters

  ↓ Glutamate ↓ GABA

- Dopamine may excitatory or inhibitory depending upon receptor subtype stimulated
  - D_1 stimulated – excitatory
  - D_2 stimulated – inhibitory

Functional circuits in Basal ganglia 00:14:46



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- Basic structure of loop

  Cortex ←
  ↓
  Striatum
  ↓
  Globus pallidus → thalamus

1. Motor loop
2. Cognitive loop
3. Limbic loop

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4.Oculomotor loop

5.Sensorimotor loop

- Has direct and indirect pathway
- Hyper direct pathway

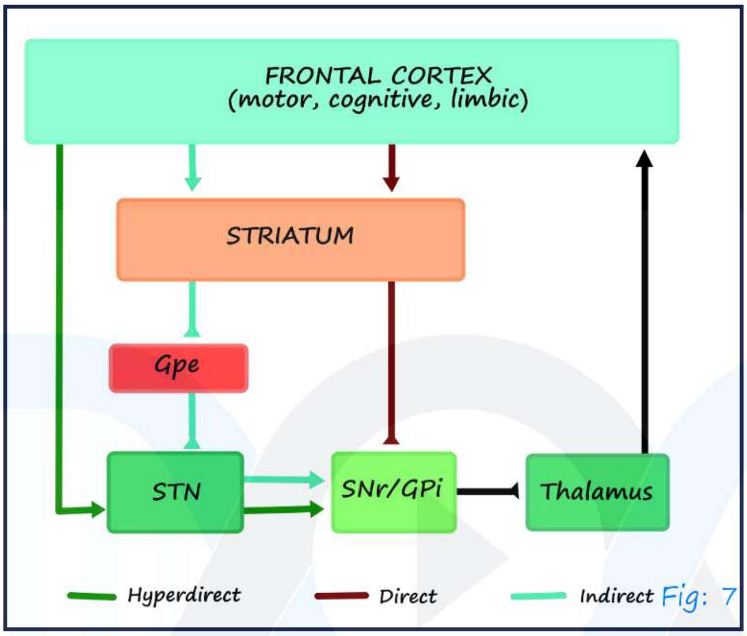


Fig: 7

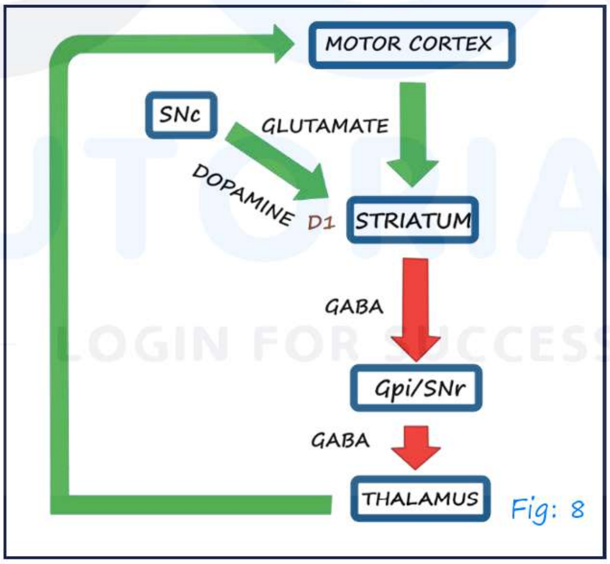


Fig: 8

- Parkinson's disease → hypokinetic
- Huntington's disease → hyper kinetic

• When direct pathway is stimulated, there occurs thalamocortical facilitation
  - Indirect pathway → thalamocortical inhibition

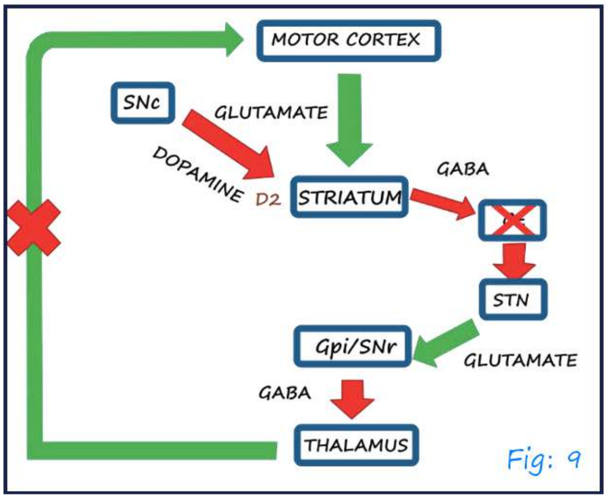
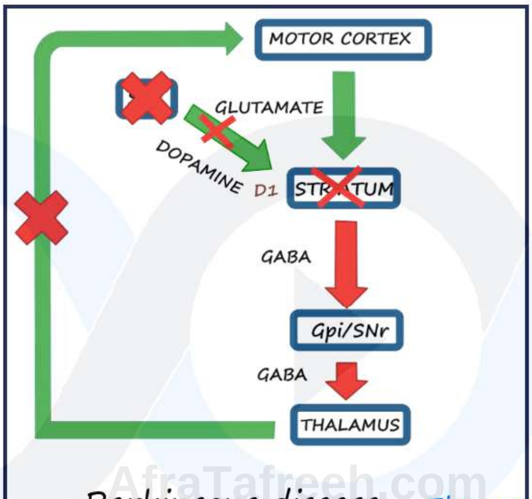
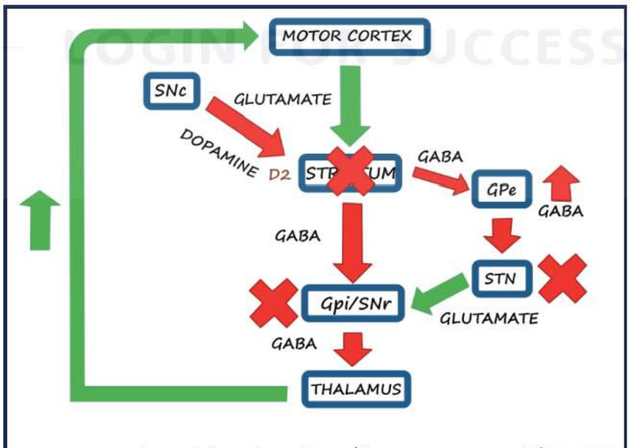


Fig: 9



Parkinsons disease Fig: 10

- In Parkinson's disease, direct pathway affected and results in thalamocortical inhibition → hypokinesia



Huntington's disease Fig: 11

- In Huntington's disease, indirect pathway is affected and results in thalamocortical facilitation → hyperkinetic movements.

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PARKINSONISM

- Disease manifestation with
  - Bradykinesia

    +

  Any one of:
  - Rigidity
  - Tremor

Causes of parkinsonism 00:01:51

- Degenerative
- Secondary

Degenerative parkinsonism 00:03:20

Idiopathic Parkinson's Disease (IDP)

75% parkinsonism

Atypical parkinsonism → parkinsonism plus syndromes

- Progressive supranuclear palsy (PSP)
- Multiple system Atrophy (MSA)
- Dementia with Lewy Bodies (DLB)
- Corticobasal Degeneration (CBD)

Others

- Wilson's disease
- Prion disease
- NBIA

Secondary parkinsonism 00:08:26

Drugs

- Neuroleptics – Antipsychotics, Metoclopramide
- Tetrabenazine
- Flunarizine
- Amiodarone
- Lithium

Toxins

- Carbon monoxide
- Cyanide
- Manganese
- MPTP: Methyl Phenyl tetrahydropyridine
- Methanol
- Hexane
- Carbon disulfide

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Others

- Infections: JE → post encephalitic parkinsonism
- NPH: Normal pressure Hydrocephalus
- Chronic liver failure

Idiopathic Parkinson's Disease 00:11:21

- 2nd Most common neurodegenerative disease
- James Parkinson discovered 'PD' in 1817
- He named it as 'Paralysis agitans'
- 'The Shaking Palsy' – Monograph

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Etiopathogenesis

- 90% → sporadic → > 50 years
- 10% → Genetic
- AD → classical age group
  - LRRK2, SNCA genes, Glucocerebrosidase (GBA)
- AR → Young
  - Parkin, PINK -1 genes

Loss of melanin laden dopaminergic neurons

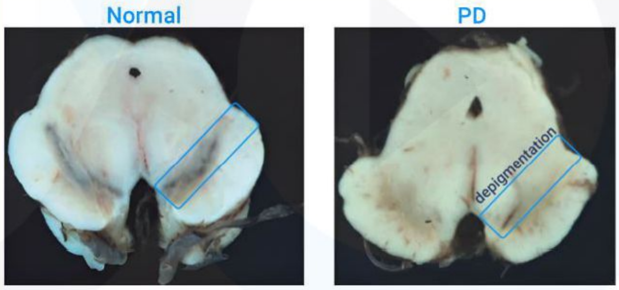

Fig: 1

- Degeneration of dopaminergic neurons in substantia Nigra pars compacta

Intraneuronal cytoplasmic eosinophilic inclusions

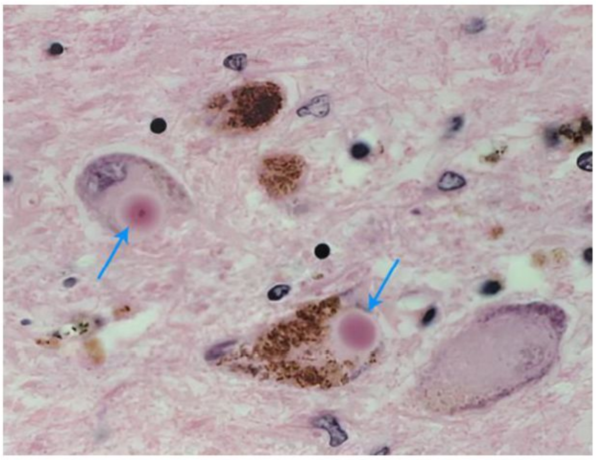

Fig: 2

Lewy Bodies → α – synuclein inclusions (pale halo)

Nigrostriatal Neurons Degeneration

↓

↓ Dopamine (major neurotransmitter) supply to striatum

↓

Manifestations of PD

Non – Dopaminergic pathology 00:24:33

- Cholinergic neurons of Nucleus Basalis of Meynert
- Nor – epinephrine neurons of Locus coeruleus
- Serotonin neurons in the raphe nuclei of brainstem
- Neurons of the olfactory system
- Cerebral hemisphere
- Spinal cord
- Peripheral autonomic nervous system

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Clinical Features 00:25:54

Cardinal or Classical manifestations	Other motor manifestations	Non motor manifestations
Bradykinesia	Micrographia	• Anosmia • Constipation } Early symptoms
Tremor (most common manifestation) - asymmetric, rest tremor 4-6 H_z, pill rolling tremor	Mask like facies (Hypo mimic facies)	Sleep disturbances RBD (enact dreams) ↓ d/t synuclein deposition
Rigidity - Extrapyramidal tract	Reduced eye blink rate	Autonomic dysfunction
Postural instability	Hypophonic voice	Cognitive impairment (late manifestation)
	Freezing	Depression
	Falls	

LOGIN FOR SUCCESS

Gait in Parkinson's Disease 00:38:56

- Initiation difficulty
- Difficulty in taking turns
- Difficulty in traversing crowded places
- Stooping forward → camptocormia
- Short steps → short shuffling gait

- Festinant gait → tendency to gain speed (acceleration)

  Catch the center of gravity

- Freezing
- Falls – usually forward

Fig: 3

Other important Gait Abnormalities 00:44:08

- High stepping gait → foot drop
- Stamping gait → sensory ataxia (DRG)

  ↓

  Defective proprioception

- Wide based/ Drunken/ Reeling gait → cerebellar
- Circumduction gait → Hemiplegia
- Waddling gait → Myopathies
- Magnetic gait → Normal pressure Hydrocephalus

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Imaging in Parkinson's Disease 00:45:55

- It is normally a clinical diagnosis
  - CT Brain & MRI Brain → rule out atypical parkinsonism
  - DaT scan

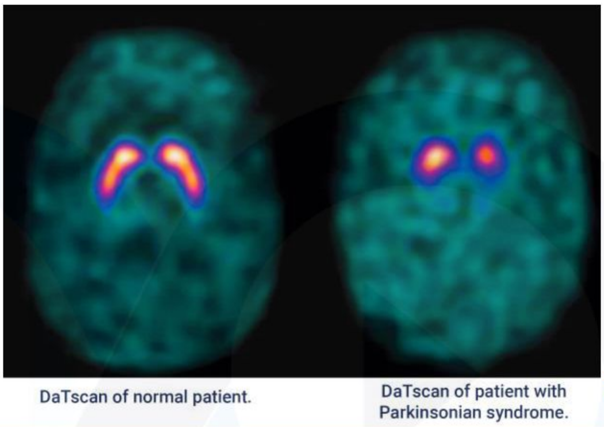

Fig: 4

- Specific type of SPECT imaging
- Using radiopharmaceutical Ioflupane I – 123 injection helps visualize dopamine transporter levels in the brain
- Differentiates PD versus Essential Tremors or Drug induced parkinsonism

Treatment of Parkinson's Disease 00:50:05

- Neuroprotective / Disease modifying treatment – Rasagiline, selegiline
- Symptomatic Treatment – Lifelong treatment

Levodopa 00:52:45

- Dopamine precursor
- Most efficacious treatment for Parkinson's Disease
  Metabolized by Dopa Decarboxylase (DDC)
- Used in combination with DDC inhibitor: Carbidopa

  LD + CD → 4:1

- Tremor – less responsive

Side effects

- Acute: Dopaminergic → Nausea, Vomiting, Postural hypotension
- Chronic: Motor complications

  ↓

  - End of dose wearing off effect as disease progresses and time of clinical effect reduces
    On – adequate dopamine
    Off – Inadequate dopamine
  - Delayed on / No – on
  - Dyskinesias

End of dose wearing off Effect 01:01:54

- Decrease dosing interval of levodopa
- Add or increase dosing of agonist
- Add MAO–B/COMT inhibitor → inhibit metabolism of dopamine

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Delayed on or No – on 01:03:12

- Ensure drug is given 30 -45 minutes before meals

Dyskinesias 01:05:06

- Ensure there is no drug abuse
- Dose reduction of levodopa
- Stop MAO–B or COMT inhibitor
- Add Amantadine
- DBS: Deep Brain Stimulation

Dopamine Agonists 01:06:30

- Agonists at Dopaminergic D_2 receptors
- Ropinirole, pramipexole → tablets
- Rotigotine → patch
- Apomorphine → subcutaneous injection
  [DOC for severe off periods] rescue therapy

Side Effects of Dopamine Agonists 01:08:16

- Nausea
- Pedal edema
- Orthostatic hypotension
- Hypersomnolence
- Hallucinations
- Impulse control disorders
  - Hypersexuality
  - Gambling

- Binge eating

- In young patients with PD with severe disability- LD
  Mild to moderate –Dopamine agonist

MAO- B Inhibitors 01:12:00

- Selegiline
- Rasagiline
- Safinamide → New drug
  - Add on drug

COMT Inhibitors 01:12:58

- Entacapone
- Tolcapone
- Opicapone – Newer drug

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Amantadine 01:13:05

- NMDA Receptor antagonist (originally antiviral agent)
- Anti-dyskinesia agent in patients with advanced PD
- Side Effects - Confusion, hallucinations, ankle edema, constipation and livedo reticularis

Anti cholinergic 01:13:53

- Trihexyphenidyl, Benztropine – central anticholinergics
- Reduce tremor and rigidity but have no effects on bradykinesia
- DOC in drug induced parkinsonism

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Watch out for anti-cholinergic side effects

- Dry mouth
- Blurring of vision
- Micturition problem

Istradefylline 01:16:08

- Adenosine receptor antagonist
  - A2A receptor

Emerging Therapies 01:16:18

- Levodopa oral inhalation powder

Fig: 5

- Apomorphine sublingual film
- Levodopa carbidopa intestinal gel → continuous dopaminergic infusion

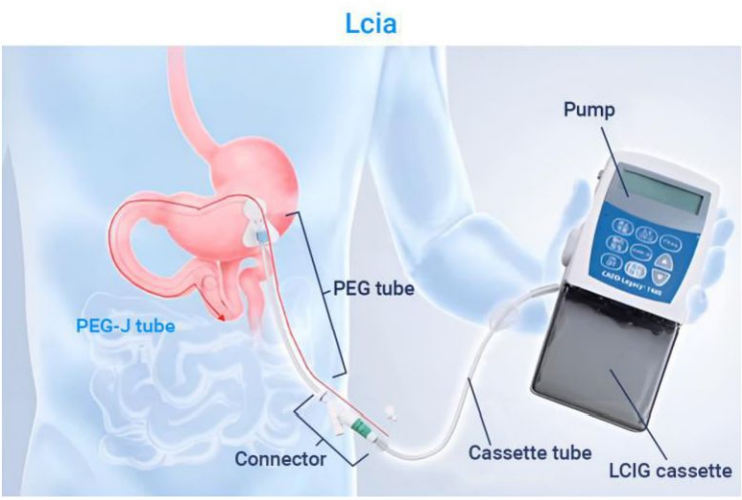

Fig: 6

Deep Brain Stimulation 01:18:15

- Electrode is placed into the target area and connected to a stimulator inserted subcutaneously over the chest wall.
- Subthalamic Nucleus – Most common
  - Globus pallidus – dyskinesias
  - Ventral Intermediate nucleus – Tremors
- Moderate to Advance PD with motor fluctuations

  (Moderate to Advance PD) After 4 years

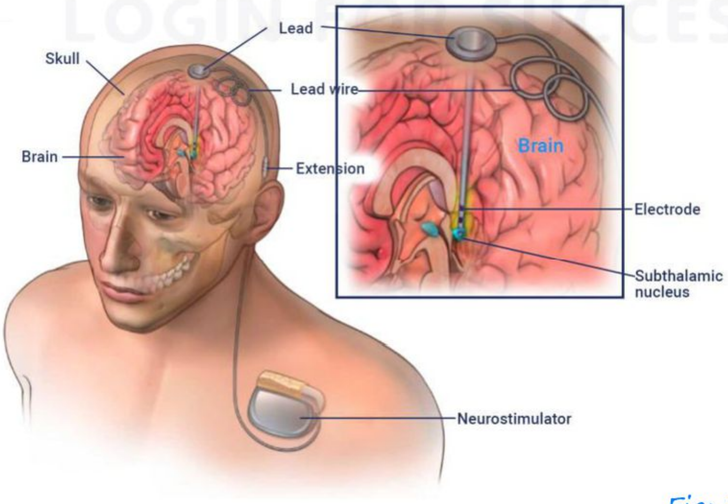

Fig: 7

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ATYPICAL PARKINSONIAN SYNDROMES

Progressive supranuclear palsy (PSP) 00:00:23

- Also known as Steele Richardson Olszewski syndrome
- Mean age of onset = 65 years

Pathology

- Structures involved
  - Mid Brain – prominent involvement
  - Globus pallidus
  - Subthalamic nucleus
  - Dentate nucleus
  - Superior cerebellar peduncle
  - Frontal cortex
- There is more wide spread degeneration (extensive) than Parkinson's.
- The abnormal protein accumulating here – tau protein → 'tauopathy'
- PSP is mostly sporadic condition
- Rarely genetic – MAPT gene mutation

Clinical features

- Brady kinesia – tremor is less prominent
- Symmetric rigidity – Axial > appendicular
- Stiff & broad-based gait
- Neck – hyper extended

- Recurrent backward falls
- Eye movements
  - Vertical gaze palsy – downward → more affected
  - Saccades – affected early
- Surprised/ astonished look
  - Due to less blink rate
  - Reptilian stare

Fig: 1

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- Cognition
  - Dementia
  - Pseudobulbar palsy – emotional incontinence– mood incongruent

↓

Due to bilateral corticobulbar fibres degeneration

Radiological findings

- MRI brain (saggital section) – severe midbrain atrophy with relatively well-preserved pons

  ↓

  'Humming bird sign' or 'Penguin sign'
- M/P ratio is decreased

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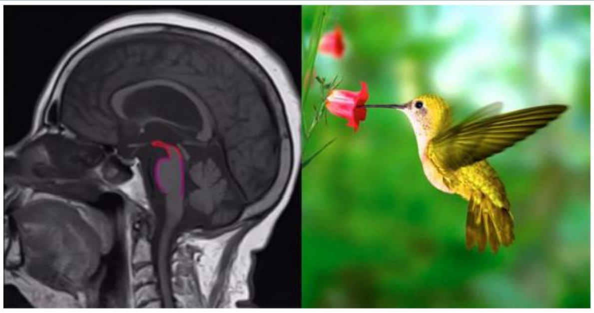

Fig: 2

- MRI brain (axial section) – 'Mickey mouse sign'– Due to mid brain atrophy

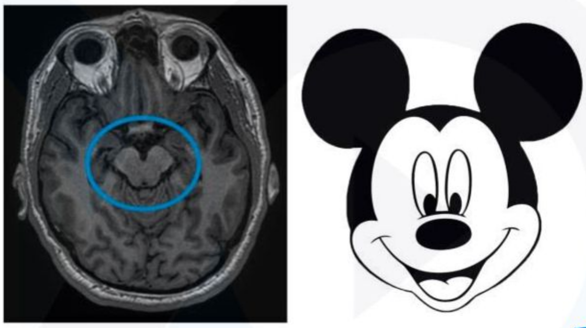

Fig: 3

Multiple System Atrophy (MSA) 00:16:08

- Two subtypes
  1. MSA – p (parkinsonian variety)
  2. MSA – C (cerebellar variety)
- Median age of onset: 55 years
- Pathology
  - Widespread degeneration
  - Structures involved
    - Substantia nigra pars compacta
    - Striatum
    - Cerebellum
    - Inferior olivary nuclei
  - Accumulation of α – synuclein protein

Clinical features

- Bradykinesia & symmetric rigidity but tremor is less prominent
- Autonomic nervous system involvement
  - Dysautonomia
  - Pre – syncopal, syncopal episodes
  - Constipation / diarrhea
  - Erectile dysfunction
  - Orthostatic hypotension
- MSA -P - parkinsonian features are prominent
- MSA – C – Cerebellar features are prominent
- Sleep disturbance – RBD – REM sleep Behavior Disorder in form of enacting dreams
- Respiratory stridor

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Radiological findings

- In an MRI of MSA – C patient
  - Cruciate hyper intensity due to involvement of Ponto cerebellar tracts degeneration
  - Hot cross bun sign

Fig: 4

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- In an MRI of MSA – P patient
  - Putaminal rim/slit sign
  - A region of hyper intensity lateral to putamen

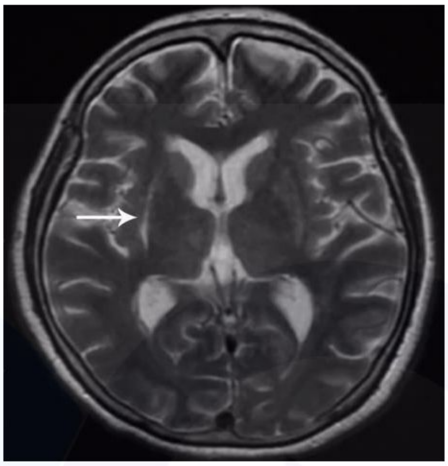

Fig: 5

Corticobasal Degeneration 00:23:36

- Uncommon among Parkinson plus syndromes
- Mean age of onset: 60 years
- Pathology - Degeneration of cortex & Basal ganglia, also tauopathy
- Also called cortico – Basal syndrome (CBS)

Clinical Features

- Bradykinesia 7 asymmetric rigidity - Tremor – less common
- Dystonia (basal ganglia degeneration)
- Apraxia
- Aphasia
- Cortical sensory loss
- Myoclonus

- Cognition – Frontal region atrophies can be seen
- Alien limb phenomenon
  - Limb assumes a position in space without the patient being aware of its location or recognizing that the limb belongs to them.
  - Happens on one side at a time
- In imaging – asymmetric atrophy of cortex & basal ganglia

Dementia with Lewy bodies 00:27:19

- Second most common cause of neuro degenerative dementia
- Mean age of onset – 75 years

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Pathology

- Structures involved specific brainstem, nuclei, substantia nigra, amygdala, cingulate gyrus, cortex.
- α –synuclein accumulation
- Extensive neuro degeneration compared to idiopathic Parkinson's disease.

Clinical Features

- Bradykinesia & symmetric rigidity
- Cognition – Dementia
  - Prominent

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- Appears first and then develops parkinsonian symptoms
- Dementia with Lewy bodies
- To differentiate: Dementia is late in parkinsonian disease
- Fluctuating cognition

- Visual hallucinations
- Sleep disturbances – RBD

Treatment of Atypical parkinsonian syndromes

00:33:26

- Poor response to levodopa
- Symptomatic management
  - Cholinesterase inhibitors – Donepezil, Rivastigmine
  - Antipsychotic
- Poor prognosis

FEATURES SUGGESTING AN ATYPICAL OR SECONDARY CAUSE OF PARKINSONISM	
Symptoms/sings	**Alternative diagnosis to consider**
History	
Early speech and gait impairment (Lack of tremor, lack of motor asymmetry)	Atypical parkinsonism
Exposure to neuroleptics	Drug – induced parkinsonism

Onset prior to age 40	Genetic form of PD
Liver disease	Wilson's disease, non-Wilsonian hepatolenticular degeneration
Early hallucinations and dementia with later development of PD features	Dementia with Lewy bodies
Diplopia, impaired down gaze	PSP
Poor or no response to an adequatetrial of levodopa	Atypical or secondary parkinsonism
Physical Examination	
Dementia as first or early feature	Dementia with Lewy bodies
Prominent orthostatic hypotension	MSA-p
Prominent cerebellar signs	MSA-C
Slow saccades with impaired down gaze	PSP
High-frequency (6-10 Hz) symmetric postural tremor with a prominent kinetic component	Essential tremor

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- Features suggesting an Atypical or secondary cause of parkinsonism

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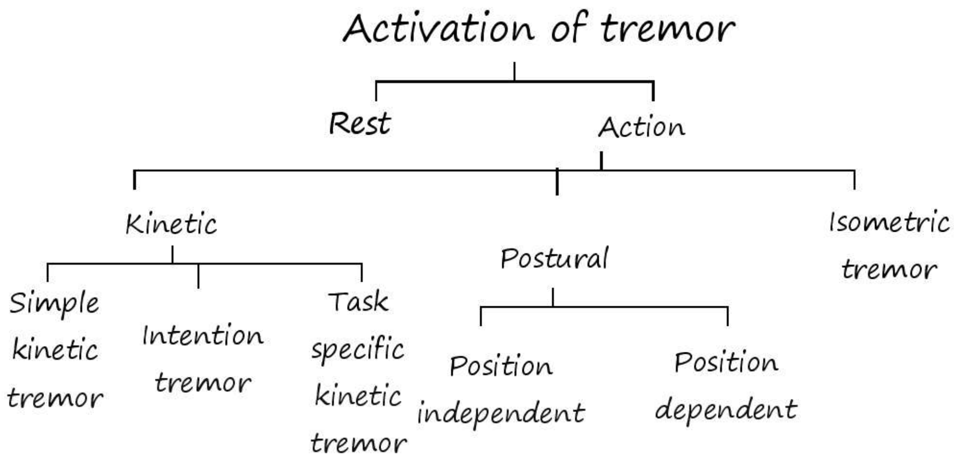
TREMOR

- Hyperkinetic movement disorders
  ↓
  - Tremor ⎤ Non jerky
  - Dystonia ⎦
  - Chorea ⎤
  - Myoclonus ⎬ Jerky
  - Tics ⎦

Tremor 00:01:32

- Most common
- Involuntary hyperkinetic disorder which is rhythmic, oscillatory
- Characterized by alternate contraction of agonist & antagonist
- Classified based on – Rest/action
  – Frequency
  – Body parts
  – Segmental
  – Generalised

Movement disorder society classification



- Classical rest tremor – Parkinson's disease
- Postural tremor – Essential tremor
- Intention tremor – Cerebellar lesions

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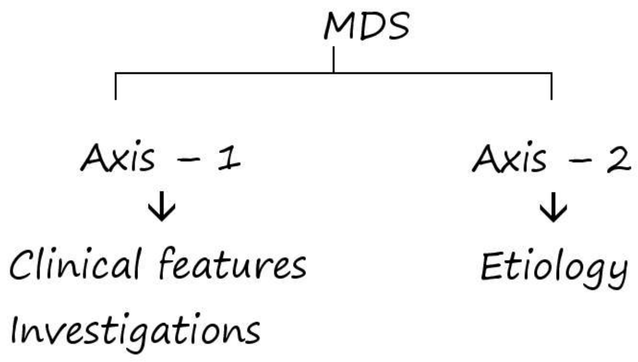
Based on frequency

- PD tremor → 4-6 Hz tremor
- Essential tremor → 6-10 Hz tremor
- Physiological tremor → 10-12 Hz tremor
- Anxiety, fatigue
  ↓
  Enhanced physiological tremor
- Orthostatic tremor (Lower limb) → 14-18Hz (Highest frequency)



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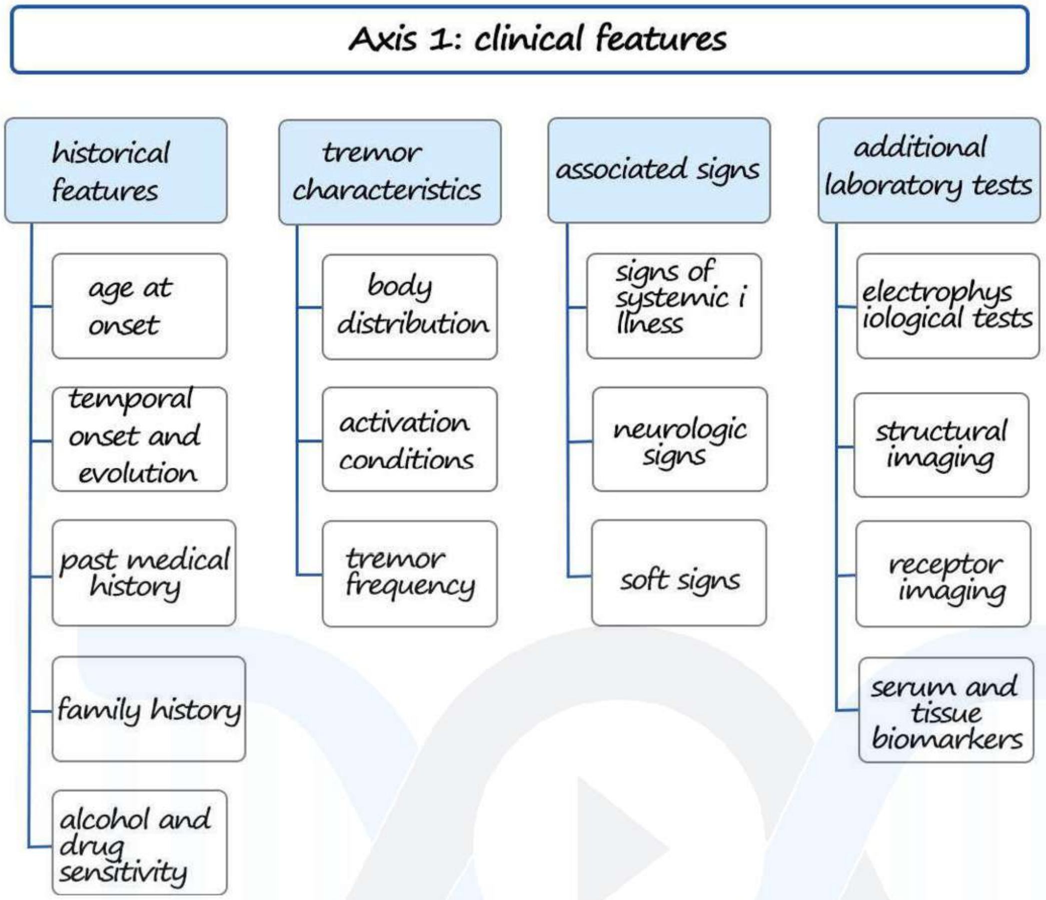

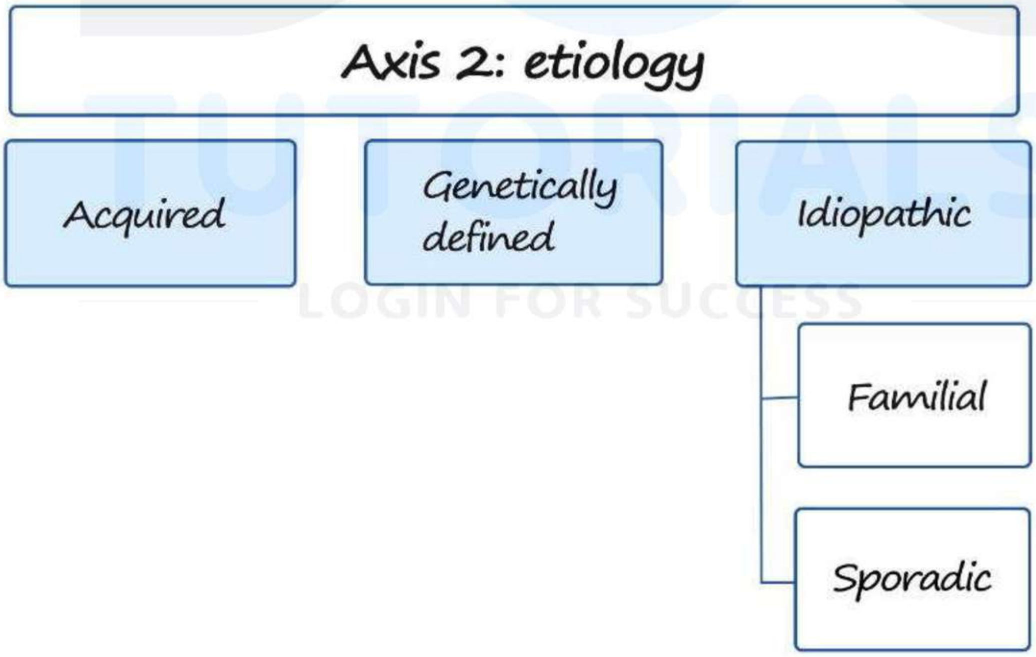

Essential tremor 00:16:06

- Starts in young age manifests 60-70years
- Bilateral symmetric tremor
- Most commonly affects UL
- Other parts: Head

  Tongue

  Jaw

  Voice tremor

  Lower limb (rare)
- Predominantly – Action tremor → Postural tremor

  Intention tremor

Diagnostic criteria of Essential tremor

i. Isolated tremor syndrome of bilateral upper limb action tremor

ii. At least 3 years duration

iii. With or without tremor in other locations (Example: head, voice or lower limbs)

iv. Absence of other neurological signs such as dystonia, ataxia or parkinsonism

- Alcohol relieves tremor
- Stress increase tremor
- Etiology: 50% family history

  Autosomal Dominant

  Pacemaker – Cerebellum

  Inferior olive

to avoid delayed cerebral ischemia

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Treatment of essential tremor

- Pharmacological treatment → Beta blocker – Propranolol

  Primidone

  Gabapentin

  Topiramate

  Clonazepam

- DBS of ventral intermediate (VIM) thalamus
- FUS → Functional ultrasound thalamotomy.

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DYSTONIA

Dystonia

- Characterized by sustained or intermittent muscle contraction causing abnormal movements, postures or both.

Characters 00:01:34

- Initiated or worsened by action
- Overflow muscle activation, co-contraction of agonist and antagonist
- Sensory trick/Geste antagonists
- Null point
- Patterned movement

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Cause of Dystonia 00:05:32

- Co-contraction of agonist and antagonist

  1.Axis I. Clinical characteristics

  Clinical characteristics of dystonia
- Age of onset
  - Infancy (birth to 2 years)
  - Childhood (3-12 years)
  - Adolescence (13-20 years)
  - Early adulthood (21-40 years)
  - Late adulthood (>40 years)
- Body distribution

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- Focal
- Segmental
- Multifocal
- Generalized (with or without leg involvement)
- Hemidystonia

- Temporal pattern
  - Disease course
- Static
- Progressive
  - Variability
- Persistent
- Action-specific
- Diurnal
- Paroxysmal
- Associated features
- Isolated dystonia or combined with another movement disorder
- Isolated dystonia
- Combined dystonia
- Occurrence of other neurological or system manifestations
- List of co-occurring neurological manifestations.

2.Axis II. Etiology

- Nervous system pathology
- Evidence of degeneration
- Evidence of structural (often static) lesions
- No evidence of degeneration or structural lesion

- Inherited or acquired
- Inherited
- Autosomal dominant
- Autosomal recessive
- X-linked recessive
- mitochondrial
- Acquired
- Perinatal brain injury
- Infection
- Drug
- Toxic
- Vascular
- Neoplastic
- Brain injury
- Psychogenic

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Treatment: -

Disease specific therapy ↓	Symptomatic treatment ↓
DRD-Levodopa Wilson's	1. Anticholinergics • Trihexyphenidyl • Benztropine 2. Baclofen • GABA agonist • Oral • Intrathecal baclofen infusion 3. Tetrabenazine • Pre-synaptic dopamine depletor • VMAT-2 inhibitor (vesicular monoamine transporter-2) 4. Antipsychotics • Chance of Parkinsonism 5. Benzodiazepines • Clonazepam 6. Botulinum toxin • Inhibits Ach release • Cervical dystonia • Blepharospasm

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<tr>
<td>Serotype A
↓
• Ona botulinum toxin
• Inco botulinum toxin
• Abo-botulinum toxin</td>
<td>Serotype B
↓
• Rima botulinum toxin</td>
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Effect of botulinum toxin lasts for 3-6 months
7. DBS
↓
Stimulation of Globus pallidus interna and subthalamic nucleus.
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CHOREA

- Derived from Greek word meaning "dance"
- Defined as hyperkinetic involuntary movement which is non-rhythmic, jerky, semi purposive movement with a random and flowing nature
- Site of lesion: - caudate nucleus.

Etiology 00:02:23

Acquired Causes of Chorea	
Category	**Examples**
Structural lesion	Vascular causes: ischemic and hemorrhagic strokes, vascular malformation (example: Moyamoya syndrome) Tumors demyelinating lesions
Metabolic/endocrine	Nonketotic hyperglycemia Hypoglycemia Hypocalcemia Hyponatremia/hypernatremia Uremia Acquired hepatocerebral degeneration Hyperthyroidism

	Hypoparathyroidism/hyperparat hyroidism
Infectious	Toxoplasmosis HIV encephalopathy Prion diseases
Drug-induced	Levodopa Cocaine ("crack-dancing) Amphetamine Anticonvulsants Lithium Anticholinergics Neuroleptic withdrawal
Autoimmune/ paraneoplastic	Sydenham chorea Rheumatologic diseases: systemic lupus erythematosus, antiphospholipid antibody syndrome, systemic sclerosis Autoimmune neurologic syndromes: anti-CRMP-5, anti-NMDA, anti-Hu (ANNA-1), anti-Yo, anti-LGI1, anti-CASPR2, anti-GAD65, anti-IgLON5
Other	Polycythemia vera

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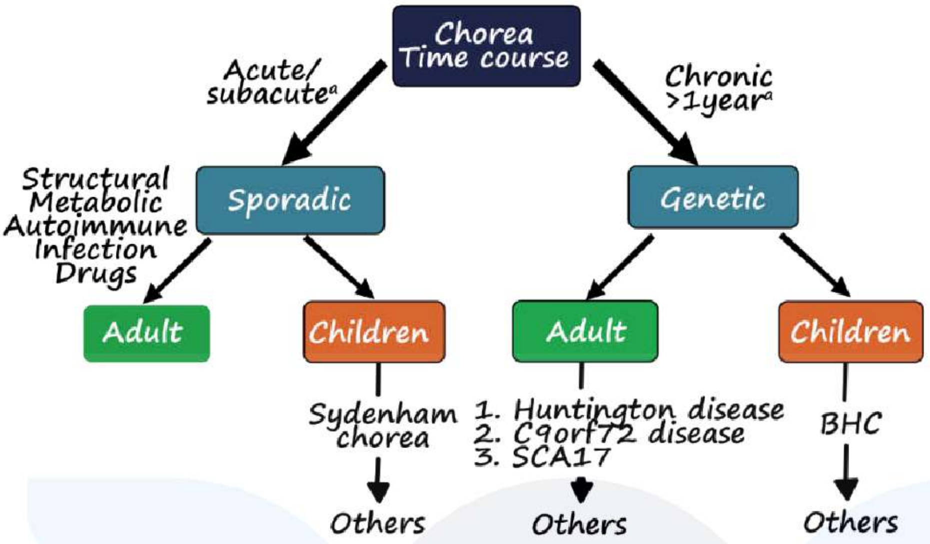
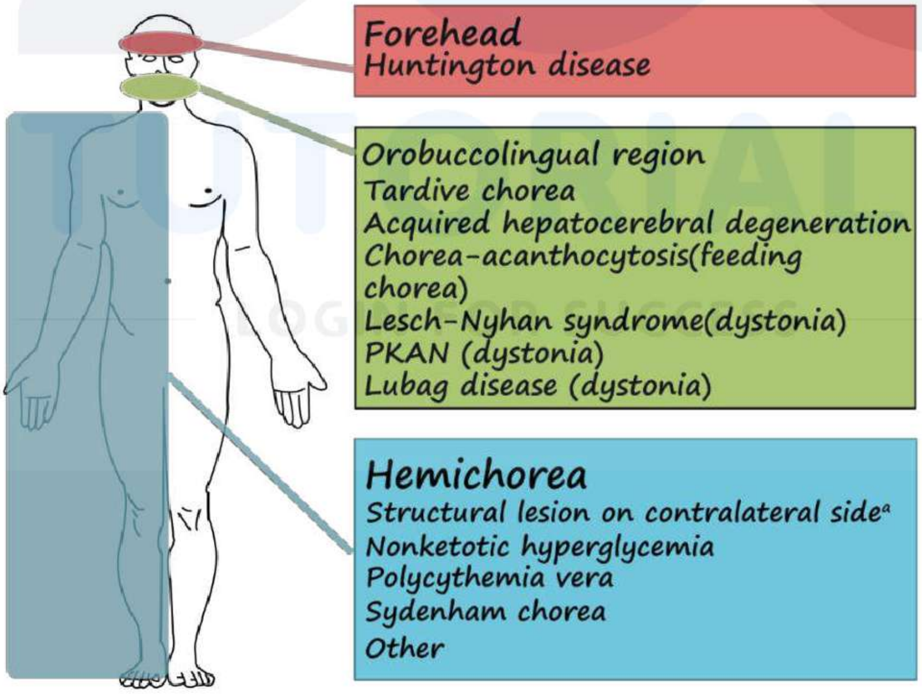
Diagnostic approach to chorea 00:07:20



- Benign hereditary chorea – most common genetic cause of chorea in children



- PKAN
  - Pantothenic kinase associated neurodegeneration
  - Belongs to NBIA

Huntington's disease 00:15:08

- First described by George Huntington
- Progressive neurodegenerative disease
- Age: - 25-45 years
- Etiopathogenesis: -
  - Trinucleotide repeat expansion disorder
  - Affects chromosome 4p [Q]
  - CAG repeat expansion
- CAG usually codes for glutamine

  Formation of polyglutamine (toxic)

  ↓

  Neuronal loss by
  - Apoptosis
  - Mitochondrial dysfunction
  - Glutamate excitotoxicity
- Loss of medium spiny neurons in striatum → atrophy of caudate and putamen
  - AD
  - Mutant gene – Huntingtin gene
- Clinical features
  - Anticipation
  - High penetrance
  - CAG repeats > 40 → disease manifests

    25-39 → intermediate
  - Motor manifestations
  - Oculomotor manifestations

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- Cognitive manifestations
- Behavioral manifestations

- Earliest oculomotor manifestation → vertical saccades (delay in initiation of vertical saccade)
- Dysarthria
- Gait dysfunction
- Chorea – reflection of hyperdopaminergic state
- Cognitive affection – subcortical dementia due to frontal

  Subcortical cognitive circuits are affected

- Behavioral abnormalities
  - Depression
  - Psychosis
  - Suicidal tendencies
- Children → Parkinsonian phenotype – Westphal variant
- Investigations
  - Imaging → Atrophy of caudate and putamen
  - Box car ventricles

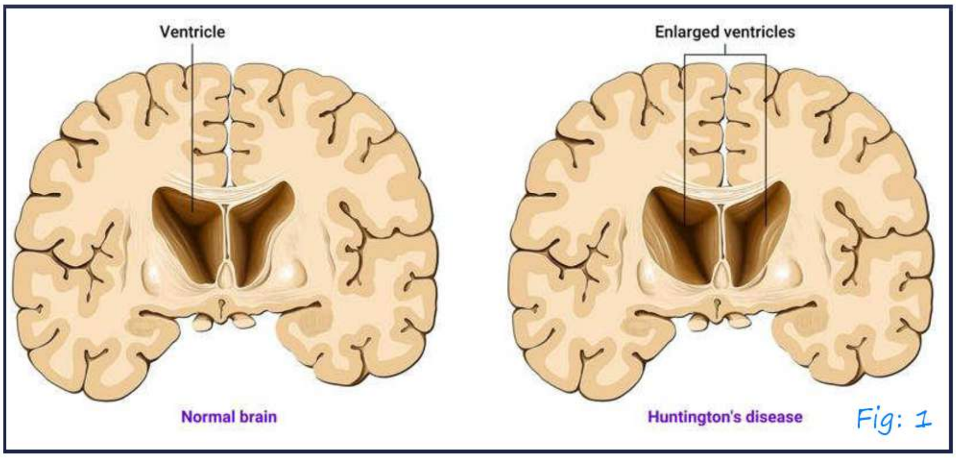

Fig: 1

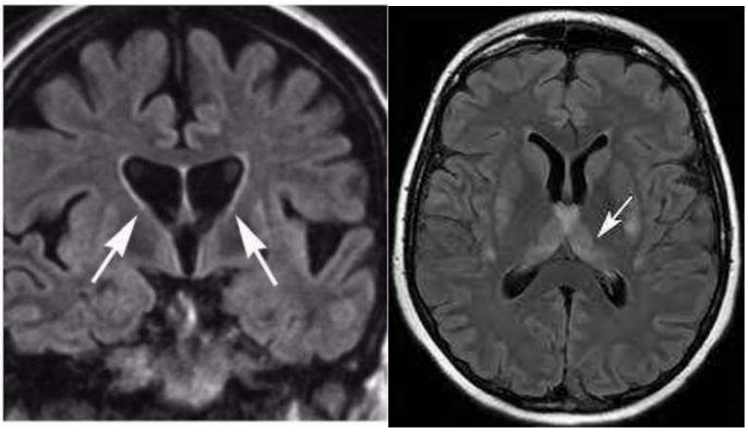

Fig: 2

- B. juvenile HD → Hyperintensity in caudate and putamen
- PET → hypometabolism in caudate and putamen
- SPECT → hypoperfusion in caudate and putamen
- Genetic testing → CAG repeats

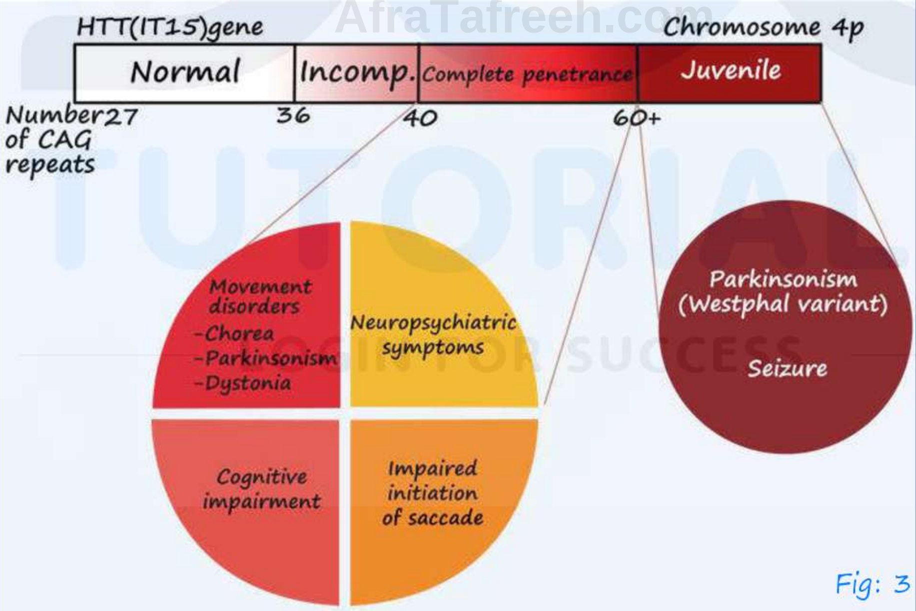

Fig: 3

- Treatment
  - No definite disease modifying therapy
  - Symptomatic therapy

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- Tetrabenazine – pre-synaptic dopamine depletor
  Inhibiting VMAT – 2
  (Vesicular monoamine transporter)
- Deutetrabenazine – Deuterated form
  - Antipsychotics
  - SSRI'S
  - Levodopa – predominant Parkinsonism features
- Research on altering mRNA is ongoing

Benign hereditary chorea (BHC) 00:42:33

- Due to mutation in NKX2-1 gene
  ↓
  Thyroid transcription factor – 1 (TTF -1)

Sydenham chorea 00:43:50

- Autoimmune chorea
- Due to group A streptococcal infection followed by 2 – 3 months
- Age: - 5-15 years
- F>M
- Also known as st. vitus dances
- Jack in the box phenomenon (lizard tongue)
- Milkmaid grip
- Echo to look for carditis
- Penicillin prophylaxis
- Treatment

- Valproate
- Carbamazepine
- Steroids
- Plasma exchange
- IV Ig

Q. Most common systemic disorder associated with chorea – SLE

Q. Most common endocrine condition associated with chorea – Hyperthyroidism.

General approaches for treatment of chorea

00:51:04

Therapeutic Options in Chorea

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- Specific Therapies
  - Blood sugar control in nonketotic hyperglycemia
  - Phlebotomy and hydroxyurea in polycythemia vera
  - Treatment for hyperthyroidism
  - Immunotherapies in autoimmune choreas
- Symptomatic Therapies
  - Pharmacologic therapies
- Presynaptic dopamine depletors
  - → Tetrabenazine and reserpine
  - → New-generation vesicular monoamine transporter 2 inhibitors
    - Deutetrabenazine

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- Valbenazine

- Postsynaptic dopamine receptor blockers (dopamine receptor blocking agents, neuroleptics or antipsychotics)
  → Typical antipsychotics
  - Haloperidol

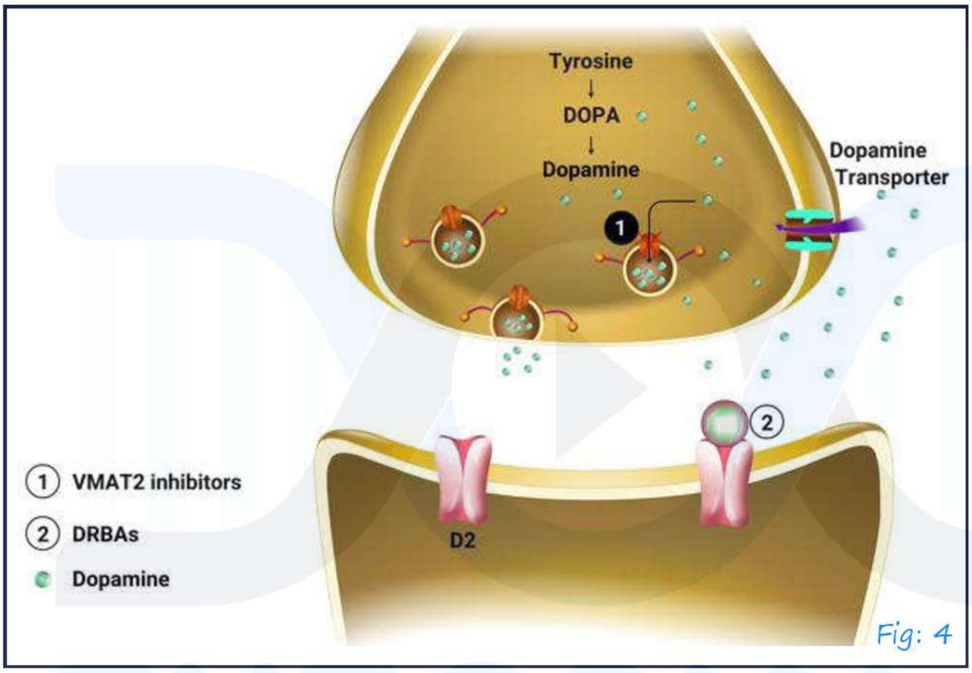

Fig: 4

- VMAT 2 inhibitors
- Dopamine receptor blocking agents → Antipsychotics → Typical and Atypical.

MYOCLONUS

Introduction 00:00:22

- Sudden, brief, shock like and jerky movements
- Occur either because of muscle contraction (positive myoclonus)

  Loss of muscle tone (Negative myoclonus)

Classifications 00:02:00

1.Classification

- Spontaneous
- Action induced
- Stimulus sensitive (reflex)

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2.Based on site

- Cortical
- Subcortical
- Brain stem
- Spinal cord

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3.Based on Distribution

- Focal
- Segmental
- Multifocal
- Axial
- generalized

4.Based on type

- Physiological

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- Hypnic jerks

- Pathological
  - Essential
  - Epileptic
  - Progressive myoclonic epilepsy
  - symptomatic
- Essential

Dystonia myoclonus

↓

Epsilon sarcoglycan gene mutation

- epileptic
  - juvenile myoclonic epilepsy (JME)
  - epilepsy partialis continua (EPC)

- progressive myoclonic epilepsy
  - unverricht lundborg disease
  - Lafora body disease
  - Neuronal ceroid Lipofuscinosis (NCL)
  - sialidosis
- symptomatic
  - post hypoxic myoclonus (Lance Adam syndrome)
  - dementing illness (Alzheimer's disease)
  - CBGD (Corticobasal ganglionic degeneration)
  - Drugs and toxins

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Treatment 00:12:24

- Treatment of underlying cause
- Clonazepam
- Levetiracetam
- Valproate
- Piracetam
  - Focal myoclonus → botulinum toxin
  - DYT-11 myoclonus → DBS (Deep brain stimulation).

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TICS

Introduction 00:00:18

- Brief, rapid, repetitive, stereotypical movements
- Jerky and non- rhythmic
- Temporarily suppress the tics

Classification

TICS
- Motor tic
  - Simple
    - eye blinking
    - Head jerks
  - Complex
    - jumping
- Vocal tic
  - Simple
    - Grunting
  - Complex
    - Echolalia
    - palilalia
    - Coprolalia

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- Echolalia- repeating others words
- Palilalia- repeating his own words
- Coprolalia- usage of obscene language

Tourette disorder 00:04:50

- Complex neurobehavioral disorders
- Age> 18 years (mean age-7 years)

- M>F
- Clinical features: motor ticks

  Vocal tics

  ADHD

  OCD

  Anxiety disorder

  Mood Disorder

- **Pathophysiology**: - combination of genetic +environmental factors

  - Basic circuit affected —corticobasal ganglia-thalamocortical circuit
  - Dopamine
  - Endogenous cannabinoids may affect
  - Pandas → pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection

Treatment

- 1 tier – behavioral therapy
- Pharmacotherapy

  1st line agents | 2nd line agents

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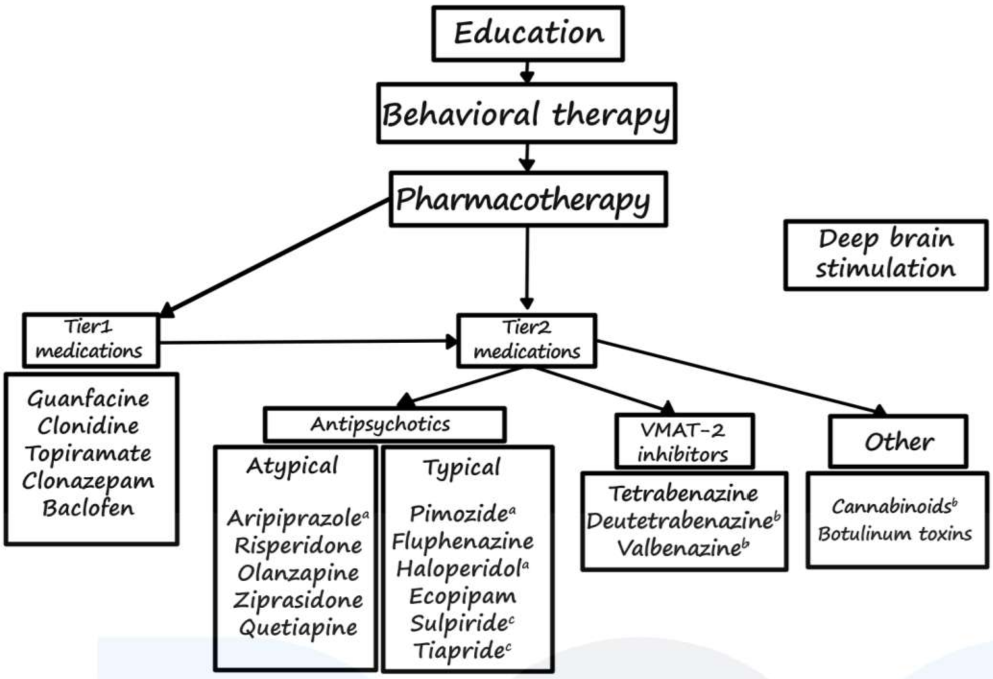

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DRUG INDUCED MOVEMENT DISORDER

Introduction 00:00:20

- Occur due to dopamine receptor blockade of central dopaminergic transmission
- Drugs – antipsychotics, Prochlorperazine, Metoclopramide — Neuroleptics
- Other classes of drugs → Amphetamine
  - Cocaine
  - Opioids
  - MDMA

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Manifestations 00:03:46

- Acute
- Subacute
- Tardive

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Acute presentation

- Dystonia – generalised in children
  - focal in adults
- Treatment: – Anticholinergics (Benztropine)
  - Benzodiazepines

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Subacute presentation

- Akathisia- motor restlessness
- Treatment: - Anticholinergics &
  Benzodiazepines

Tardive/ late presentation

- Months – years
- Tardive dystonia, dyskinesia, akathisia, tics, myoclonus
- May persist even after stopping the drug

TARDIVE DYSKINESIA

↓

Affects- mouth, Lips, Tongue

→ Typical antipsychotics (m/c)

→ Atypical antipsychotic

↓↓

On prolonged use

↓

Dopamine receptor super sensitivity or upregulation

- Treatment: - 2 FDA approved agents
  ↓
  Deuterobenazine
  Valbenazine
- EMERGENCIES → Neuroleptic malignant syndrome
  → Serotonin syndrome

Neuroleptic malignant syndrome 00:13:14

- Clinical features: - Fever
  Rigidity
  Altered sensorium
  Autonomic disinfection
- Investigation: - S. CPK increased
- Complications: - Rhabdomyolysis
  Aspiration pneumonia
  Renal failure
- Treatment: - Aggressive management
  ↓
  - Bromocriptine (Dopamine agonist)
  - Levodopa
  - Dantrolene sodium
  - Benzodiazepines
  - IV fluids, correction of electrolyte imbalances

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Serotonin syndrome 00:17:10

- Due to usage of drugs that enhance serotonergic transmission
  - Linezolid
  - Triptans
  - Lithium
- Clinical Features: - Fever, Rigidity
  Altered sensorium
  Myoclonus
- Treatment: - Aggressive management
  - Cyproheptadine (serotonin antagonist)
  - Benzodiazepines.

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RESTLESS LEG SYNDROME

- As per ICSD-3, belongs to sleep related movement disorders

Clinical features 00:01:18

- Urge to move the limbs
- Rest worsens the urge
- Evening/ night worsens the urge
- Disappears on getting up and moving
- Sensorimotor syndrome
- Also referred to as Willis-Ekbom syndrome
- 80% cases → PLMS (Periodic Limb Movements in Sleep)

RLS

- 1° → 50% family history mean age – 27years
- 2° → Iron deficiency, Renal failure, Pregnancy

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Investigations 00:06:10

- Clinical diagnosis
- Polysomnography

Treatment 00:06:44

- FDA approved
- Dopamine agonists
  i. Ropinirole
  ii. Pramipexole
  iii. Rotigotine
- Gabapentin enacarbil
- Vibratory counter stimulation device.

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WILSON'S DISEASE

Wilson's disease 00:00:25

- Dr Samuel Alexander Kenier Wilson published a thesis paper on "progressive lenticular degeneration"
- Autosomal recessive
- Mutation in ATP 7B gene → 13 chromosomes

  ↓

  Copper transporting P type ATPase
- Role of ATPase →

  Incorporation of copper into apoceruloplasmin

  ↓

  Ceruloplasmin not formed

  ↓

  Defective copper excretion

  ↓

  Oxidative damage

  Free radical formation

  Mitochondrial dysfunction
- In blood → decreased level of copper and ceruloplasmin

Clinical manifestations 00:05:44

- Neurologic
- Psychiatric
- Ophthalmologic

- Hepatic
- Musculoskeletal

Neurological presentations

- Dystonic syndrome
- Ataxic syndrome
- Parkinsonian syndrome
- Tremor syndrome → wing beating tremor

Ophthalmology manifestations

- Copper deposition in descemet's membrane

  ↓

  KF ring formation – 90% B/L
- Copper deposition occurs superiorly and inferiorly
- Sunflower cataract.

Investigations 00:11:02

- Hb-Coomb's negative hemolytic anemia
- $\frac{AST}{ALT} > 1$
- S. Ceruloplasmin ↓↓
- 24-hour urinary copper ↑↑ (>100 mcg/day)
- Liver biopsy

  (Best diagnosis) > 250mcg/g dry weight, copper
- Imaging: -

  - Face of giant panda

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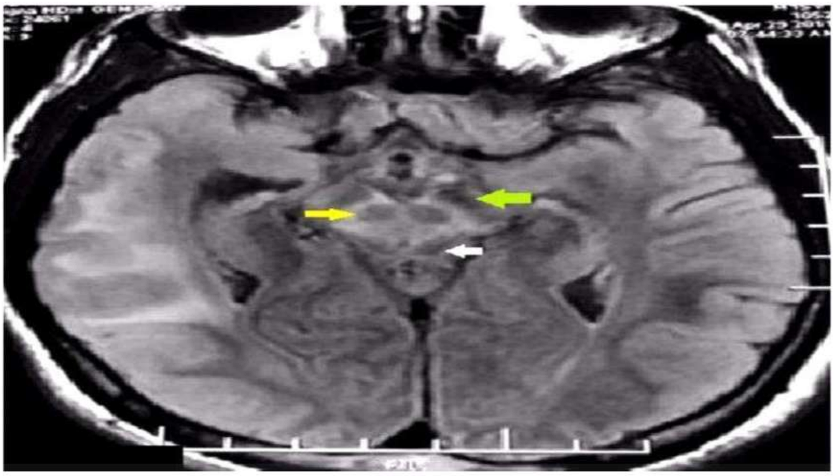

Fig: 1

- Face of miniature panda appearance

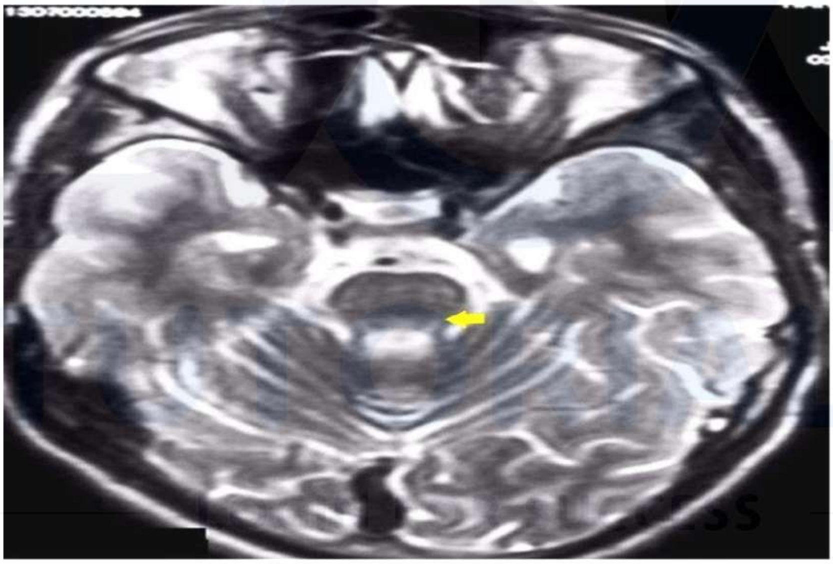

Fig: 2

- Bright claustrum sign

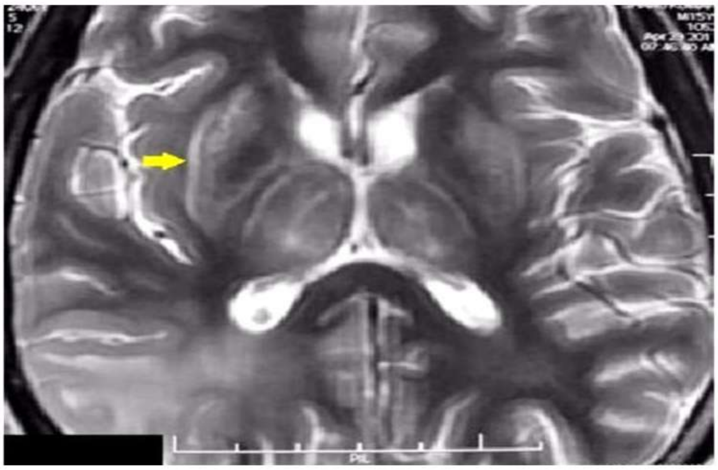

Fig: 3

- Mercedes benz sign – CPM like

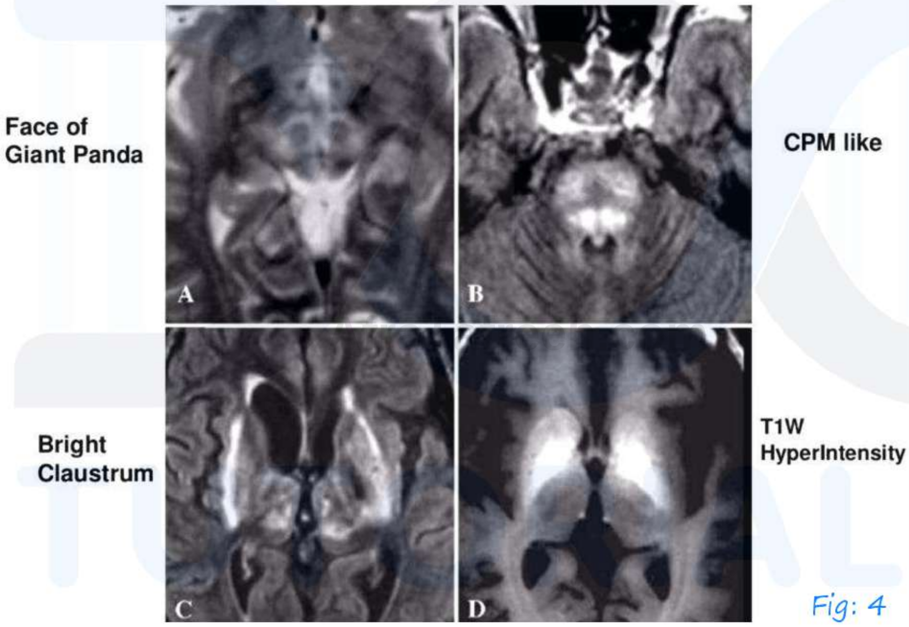

Fig: 4

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Treatment 00:18:52

- Zinc – first choice — Lifelong therapy
  - D – penicillamine
  - Tetrathiomolybdate
  - Trietene
- Carriers do not require treatment

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NBIA

NBIA 00:00:40

- Neurodegeneration with brain iron accumulation
- Iron deposition (prominently in basal ganglia)
- Clinical Features: -
  - Extrapyramidal features
- Chorea
- Dystonia
- Parkinsonism
  - Pyramidal dysfunction
  - Psychiatric features
  - Ophthalmologic features (retinal degeneration)
  - Cognitive disturbances

Types of NBIAs 00:03:18

1.PKAN (AR) – Pantothenate Kinase Associated Neurodegeneration

↓

Gene mutated – PANK2 gene 50% of NBIA's

- Previously known as Hallerverden Spatz disease

Fig: 1

- Eye of tiger sign
- Hypo intensity in globus pallidus

  ↓

  Iron deposition
- Hyperintensity → Gliosis

2.PLAN – PLA 2 G6 Associated Neurodegeneration, AR

3.MPAN – Mitochondrial Membrane Protein Associated Neurodegeneration

4.COPAN – Co A Synthase associated neurodegeneration

5.FAHN – Fatty Acid Hydroxylase associated Neurodegeneration

6.BPAN – Beta Propeller associated neurodegeneration, x-linked inheritance

7.Neuro ferritinopathy (AD)– occurs due to ferritin light chain mutation

8.Aceruloplasminemia – associated with DM

9.Wood house sakati syndrome

10. Kufor rakeh syndrome.

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ALZHEIMER'S DISEASE

- Cognition – acquire and manipulate knowledge
  - Mild Cognitive Impairment (MCI)
  - Dementia

  New terms(DSM-5):
  - MCI – Minor neurocognitive disorder
  - Dementia – Major neurocognitive disorder

DSM-5 criteria for major neurocognitive disorder (Previously dementia)
A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains*: - Learning and memory - Language - Executive function - Complex attention - Perceptual-motor - Social cognition
B. The cognitive deficits interfere with independence in everyday activities. At a minimum, assistance should be required with complex instrumental activities of daily living, such as paying bills or managing medications.
C. The cognitive deficits do not occur exclusively in the context of a delirium
D. The cognitive deficits are not better explained by another mental disorder (eg, major depressive disorder, schizophrenia)

- Perceptual motor – involves sensory + motor
- Social cognition – judging another person's mood/ behavior
- Depression is also referred to as Pseudo dementia

Alzheimer's disease 00:10:12

- Most common cause of dementia
- Elderly (>70 years)

Epidemiology and risk factors 00:11:30

- Age
- Positive family history
- Females
- Low socio-economic status
- Trauma
- Apo and allele
  - Apo E gene on chromosome 19
  - Apo E_2, E_3, E_4 ⊕
  - Apo E_4 increases AD risk [Q] (2-3-fold)
  - Apo E_2 decreases AD risk [Q]
- DM
- HTN
- H/O CVA
- Dyslipidemia
- Hyperhomcystinemia
- Low serum folate

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- Smoking
- Alcoholism
- Decreased intake of fruits

Pathogenesis 00:14:46

- Neurodegenerative disease
- Predominantly affects temporo-parietal lobes
- Degenerative changes start especially in medial temporal lobe with includes entorhinal cortex, peri-rhinal cortex and hippocampus
- Then involves lateral temporal lobe and parietal lobe, frontal lobe

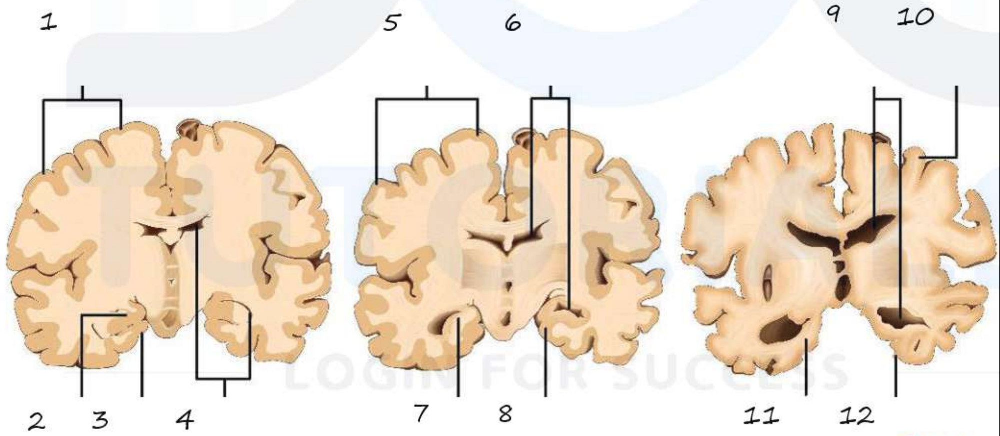

Fig: 1

1. Cerebral cortex
2. Hippocampus
3. Entorhinal cortex
4. Ventricles
5. Shrinkage of cerebral cortex
6. Moderately enlarged ventricles
7. Shrinkage of the hippocampus
8. Shrinkage of entorhinal cortex
9. Severely enlarged ventricles
10. Extreme shrinkage of cerebral cortex
11. Extreme shrinkage of hippocampus
12. Extreme shrinkage of entorhinal cortex

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Neuropathological features

- Neuritic plaques
- Neurofibrillary tangles
- Amyloid accumulation in blood vessel wall of cortex and leptomeninges
  - There occurs accumulation of amyloid – soluble amyloid species – oligomers
  - Problematic amyloid – $A\beta_{42}$
  - In neuritic plaques, there is polymerization of amyloid (Aβ) → accumulation of amyloid with core → Aβ, Apo E and also certain proteoglycans

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- Older the AD patient, more the number of neuritic plaques

Neurofibrillary tangles (NFT)

- Accumulation of hyperphosphorylated tau proteins
- Tau – Tubulin associated unit
  - Stabilizing microtubules → Normally involved in axonal transport

- When axonal transport is interfered with

↓

Cell death and neurodegeneration

- Aβ amyloid gets deposited in blood vessels

↓

Amyloid angiopathy

Biochemical problem 00:23:46

- Acetylcholine
  - Major production in nucleus basalis of Meynert located in basal forebrain
- Norepinephrine
- Serotonin

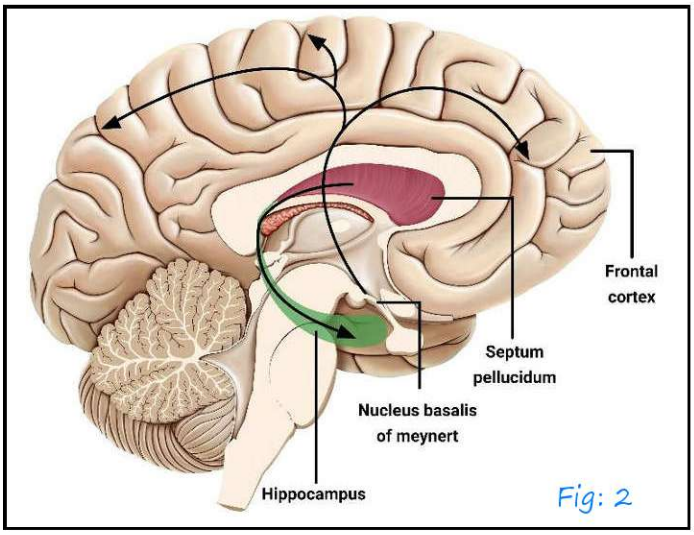

Fig: 2

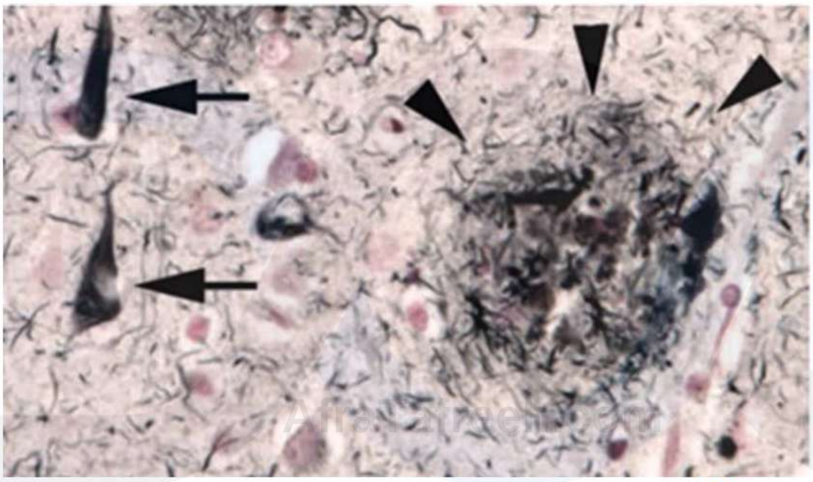
Fig: 3

Neuritic plaques

↓

Associated with aging

↓

Neurofibrillary tangles → associated with AD severity[Q]

- **Step 1:** Cleavage by either α or β secretase

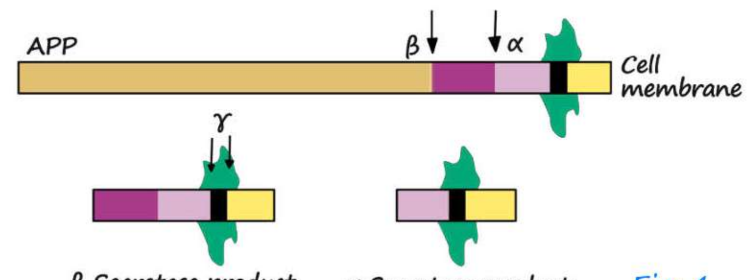

Fig: 4

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- **Step 2:** Cleavage by γ secretase

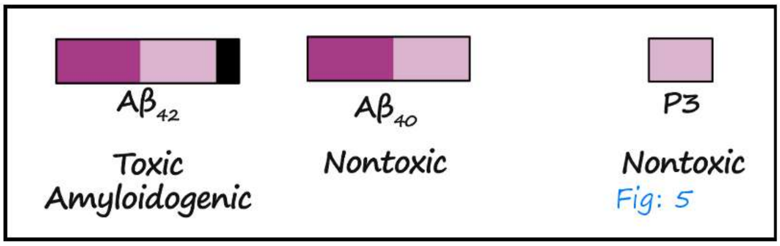

Fig: 5

- Aβ is formed form amyloid precursor protein

Genetics 00:27:46

- Predominantly sporadic
- APP – Chromosome 21
  - Individuals with down's syndrome are likely to develop Alzheimer's disease
- Presenilin-1-chromosome 14
  - Most common genetic mutation in familial early AD
- Presenilin 2 – chromosome 1
- Apo E – Chromosome 19

Clinical features 00:30:20

- Slowly progressive cognitive decline

Classical AD → Late onset dementing illness

Order of affection → Memory → language → visuospatial function → executive function

AD variants

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- Memory → Episodic memory loss[Q]

Memory

Working →
- Temporary storage and manipulation
- Frontal lobe

Episodic →
- Personal events
- Medial temporal lobe (papez circuit)

Semantic →
- Facts and knowledge
- Inferolateral temporal lobe

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- Language

  ↓

  Naming → Comprehension → fluency affected

  – Common in Alzheimer's – Anomic aphasia
- Visuospatial

  ↓

  Navigation function
- Executive function

  ↓

  Cognitive domain that you want for planning and programming complex goal directed activities
- Initially MCI, later progresses to AD
  - Psychiatric manifestations
  - Myoclonus
  - Bed ridden

AD variants 00:43:10

- Posterior cortical atrophy variant
- Logogenic aphasia
- Frontal variants

i. Posterior cortical atrophy

- Occipital and parietal regions involved

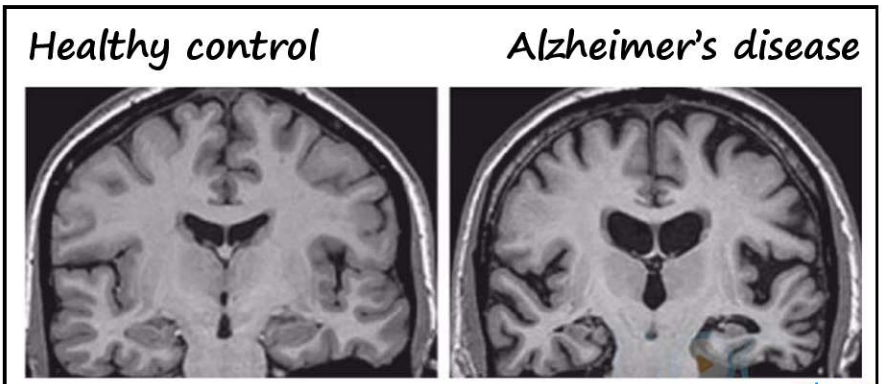

Fig: 4

Posterior cortical atrophy

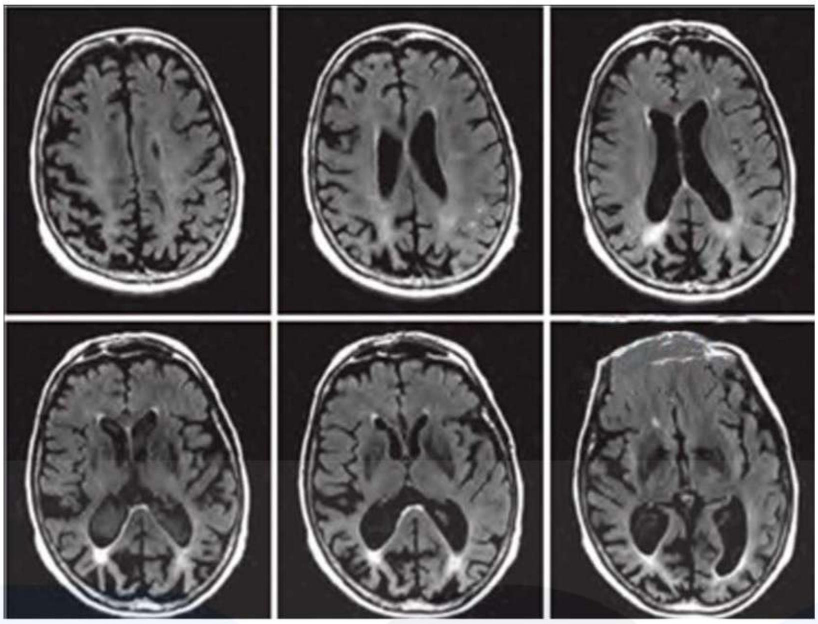

Fig: 5

ii. Logogenic aphasia

- Naming and repetition

iii. Frontal variant

- Dysexecutive syndrome

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Biomarkers 00:47:30

- CSF $A\beta_2$ decreased in AD
- CSF Tau
  - t-tau ⎤ Increased
  - p-tau ⎦
- Imaging – Structural imaging – median temporal atrophy

  Functional imaging
  - FDG PET → hypometabolism
  - Amyloid PET ⎤ Abnormal deposition
  - Tau PET ⎦

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Treatment 00:52:08

Treatment

Medical | **Supportive**

- Medical → Acetylcholinesterase inhibitors
  - Donepezil (5mg-10mg) → often preferred drug
  - Rivastigmine
  - Galantamine
  - Tacrine → not used now due to hepatoxicity

NMDA receptor antagonist
↓
Memantine

- Mild-moderate → Donepezil
- Moderate-severe → Donepezil + Memantine
  - Researches going on → Aβ 42 vaccination
    → Monoclonal antibodies
    ↓
    Solanizumab

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VASCULAR COGNITIVE IMPAIRMENT

VCI 00:00:17

- Previously called vascular dementia
- Due to affection of blood vessels
- Often occurs in elderly individuals with vascular risk factors like DM, HTN, smoking, alcohol, dyslipidemia
- Small vessel dementia
  - Binswanger's disease
  - Subcortical arterosclerotic leukoencephalopathy
- Dementia due to
  - Microinfarcts
  - Large infarcts
  - Micro bleeds
  - Large bleeds
  - Ultimately it is Either due to
    1. HTN
    2. Cerebral Amyloid angiopathy

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Strategic infarcts

- Thalamus
- Basal ganglia
- Angular gyrus

Binswanger's — executive dysfunction

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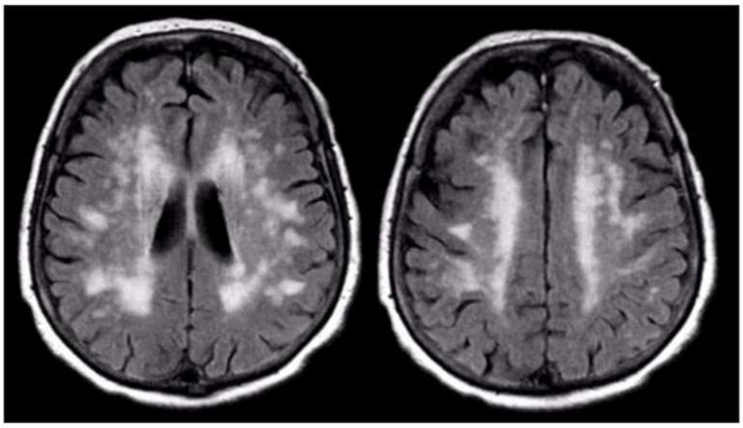

Fig: 1

Treatment of VCI

- Treatment of vascular risk factors
- Mixed dementia – Alzheimer's disease + Vascular cognitive impairment

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FRONTOTEMPORAL DEMENTIA

- Previously called pick's disease not used now until autopsy finding shows pick bodies
- Age: 5th – 7th decade

Clinical features 00:01:32

- Clinical features: 3 variants

 1.Behavioral variant most common

 2.Semantic variant primary progressive aphasia (PPA)

 3.Non-fluent/Agrammatic variant PPA

Behavioral symptoms

- Disinhibition
- Apathy
- Personality change

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Pathology 00:04:20

- Abnormal proteins deposition in the neurons
  - TDP-43 (Most common)
  - Tau
  - FUS

Genetics of FTD 00:05:14

- C9ORF72 gene mutations
- MAPT
- GRN

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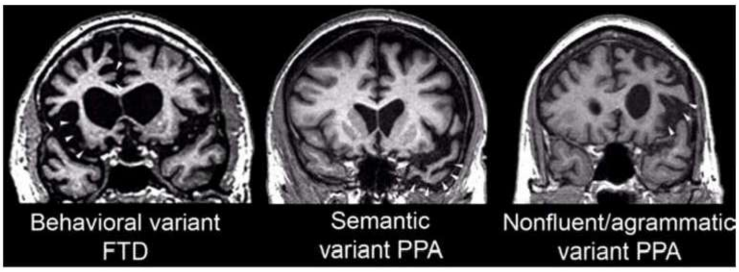

Fig: 1

- Behavioral variant – Atrophy at medial & orbital frontal
- Semantic variant – Atrophy at anterior temporal region
- Non fluent variant – Atrophy at frontal opercular region & dorsal insula

Treatment 00:07:54

- Treatment – Supportive treatment – SSRI's

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PARKINSONIAN DEMENTIAS

- Group of disorders with parkinsonism and dementia
- Includes:
  - Dementia with lewy bodies (DLB)
  - Parkinson disease dementia
  - Progressive supranuclear palsy
  - Multiple system atrophy
  - Cortico basal degeneration

Parkinson disease dementia 00:02:24

- Dementia that occurs in late course of Parkinson disease

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Dementia with lewy bodies 00:03:02

- PDD and Dementia with Lewy bodies together called as Lewy body Dementias
- Disease Often begins as dementia (or) Dementia + parkinsonism
- Core clinical features: – fluctuating cognition (Executive dysfunction, visuospatial dysfunction)
  - visual hallucination

  RBD (REM sleep behavior disorder)

  ↓

  Enact dreams

  Synucleinopathy

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Parkinsonism

- Other features: -
  - Neuroleptic sensitivity
  - Syncopal episodes
  - Postural instability → recurrent falls
  - Hyposmia
  - Apathy, depression
- Disease progression

  Enteric nervous system to olfactory system

  ↓

  Brain stem

  ↓

  Limbic region

  ↓

  Cortex
- Treatment of DLB
  - Dopaminergic medications – levodopa (not of much benefit)
  - Pimavanserin
  - Quetiapine
  - Clozapine
  - Cognitive problems – acetyl cholinesterase inhibitors

    ↓

    Rivastigmine.

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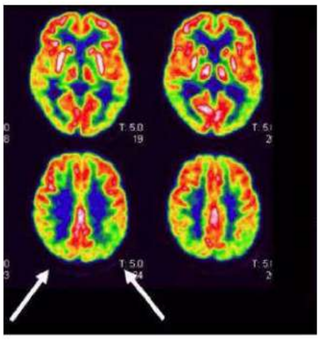

Fig: 1

FDG – PET

↓

Hypometabolism in occipital cortex with relative sparing of posterior cingulate region

↓

Cingulate island sign.

Clinical Features of Selected Parkinsonian Dementias	
Subtype	Key clinical findings
Dementia with Lewy bodies	Fluctuations/hypersomnolence Parkinsonism Visual hallucinations REM sleep behavior disorder
Progressive supranuclear palsy	Supranuclear gaze palsy Axial rigidity, Gait disorder/frequent falls Bulbar symptoms
Corticobasal syndrome	Asymmetric apraxia, dystonia, myoclonus, Cortical sensory findings, alien hand/limb, Rigidity
MSA-C/P	Ataxia, parkinsonism, long tract signs, autonomic dysfunction

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NORMAL PRESSURE HYDROCEPHALUS

CSF Circulation 00:00:54

- CSF circulation

  Choroid plexus
  ↓
  Lateral ventricle
  ↓ Foramen of munro
  Third ventricle
  ↓ Aqueduct of sylvius
  IV ventricle
  ↓ Foramen of luschke & magendie
  Subarachnoid space
  ↓ Arachnoid villi
  Dural venous sinuses

- Pulsatile arterial flow helps in CSF circulation.
- Normally CSF production – 550ml/day
- At a given time – 150ml present in ventricular system

Pathogenesis 00:03:40

- Exact pathogenesis is unknown
- Decreased CSF absorption at arachnoid villi

  ↓
  CSF pressure increases
  ↓
  Ventricle enlarges → CSF pressure normalizes

- When ventricles enlarging, there is a centrifugal force

- 65% of CSF is located in cerebral subarachnoid space
  20% of CSF is located in ventricular system space
  15% of CSF is located in spinal subarachnoid space

Clinical features

- G – Gait impairment
- U – Urinary Symptoms
- D – Dementia

- Gait impairment – wide base
  Short steps
  Difficulty in turning
- DD for NPH gait – Parkinsonian gait

DD for NPH gait	Parkinsonian gait
↓	↓
UL spared	UL swing reduced
No festination	

- NPH gait also k/as Frontal gait
  Brun's ataxia
  Gait apraxia
  Magnetic gait
- Urinary symptoms – Urgency
  Frequency
  Urinary incontinence
- Dementia – subcortical dementia
  ↓
  d/t pressure effects on cognitive circuit

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Frontal lobe ← Thalamus
↓
Basal ganglia → Thalamus

- Executive dysfunction
- Psychomotor slowing

- Age – 5th – 7th decade

Diagnosis 00:12:56

- Diagnosis
  i. History
  ii. Radiology

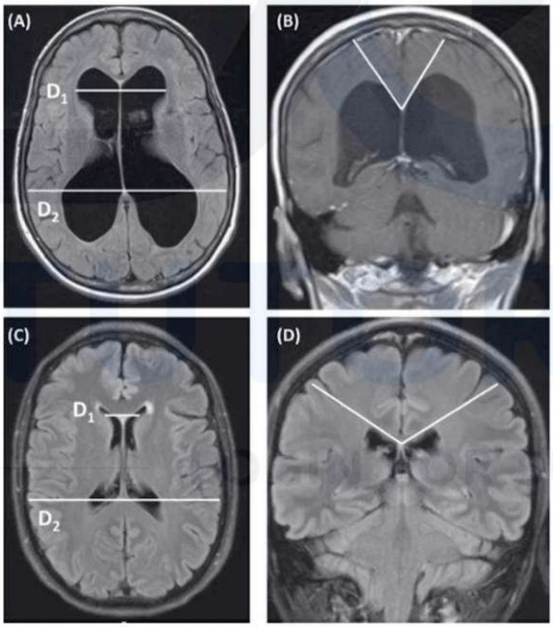

Fig: 1

- Evan's index – Ratio of maximum diameter of frontal horn to maximum internal diameter of skull @ same level. (D1/D2)
  ↓
  - >0.3 → NPH

- It helps differentiate ventriculomegaly in Alzheimer's disease from NPH
- In Alzheimer's disease it is due to cerebral atrophy

- Callosal angle – Narrow/Acute → NPH
  In normal → Obtuse

iii. CSF tap rest

↓

LP study → 30 ml CSF removed

↓

After 30 mins

↓

Ask patient to walk [compare gait]

Treatment 00:21:06

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- Form of reversible dementia
- VP shunt
  - CSF diversion
  - Done only in those who show response in CSF tap test
  - Gait improves

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CORTICAL VERSUS SUBCORTICAL DEMENTIAS

Cortical Vs Subcortical 00:00:40

Cortical dementia	Subcortical dementia
• Alzheimers disease • Frontotemporal dementia	• PSP • HIV • Normal pressure hydrocephalus

Features	Cortical dementia	Subcortical dementia
Typical example	Alzheimer's disease	Progressive supra-nuclear palsy
Basic functional deficit	Specific deficits (Apraxia, Agnosia, Aphasia)	Impaired information processing and function
Memory impairment	Poor recognition, learning deficit	Recall aided by cues, retrieval deficit
Neuropsychiatric symptoms	Depression uncommon	Depression, apathy

Motor symptoms	Uncommon	Extrapyramidal symptoms, dystonia, increased tone
Lesion	Cortical association areas and mesiotemporal limbic system	Subcortical structures and fronto-sub-cortical circuitry
Speed of cognition	Normal	Slow
Speech	Normal	Abnormal (hypophonic, mute, dysarthric)
Language	Aphasic	Normal

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REVERSIBLE DEMENTIAS

Reversible dementia 00:00:54

- Drug toxicity
  - Alcohol, heavy metals, carbon monoxide
- Metabolic
  - Hepatic/renal insufficiency, Wilson's Disease
- Trauma
  - Chronic sub-dural hematoma
- Neurologic
  - Multiple sclerosis, tumor,
  - normal pressure
  - hydrocephalus
- Infectious process
  - Chronic meningitis – fungal, TB, syphilis, HIV, Creutzfeldt-Jakob disease
- Collagen vascular disease
  - SLE, sarcoidosis
- Endocrine disorder
  - Thyroid, Parathyroid
- Nutritional deficiency
  - Vitamin B12, thiamine, folate

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PRION DISEASES

Introduction 00:00:28

- Prions are proteinaceous infectious particles, devoid of nucleic acid
- Normal conformation → abnormal conformation

  $Pr\ P^{c}$ → $Pr\ P^{sc}$

  (cellular form) (Scrapie)

  α helical structure β pleated structure
- Alzheimer's → A β amyloid

  Parkinson's, MSA → α – synuclein

  FTD → Tau

Prion diseases

- Humans
  - CJD
  - GSS
  - FFI
  - Kuru (fore tribe)
- Animals
  - Scrapie
  - Bovine spongiform Encephalopathy
  - Feline spongiform Encephalopathy
  - Transmissible mink Encephalopathy
  - Chronic wasting syndrome

- GSS – Gerstmann Strausster Scheinker Syndrome
- FFI – Fatal familial insomnia

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Cruetzfeldt Jakob Disease (CJD)

- Subtypes: -
  - Sporadic CJD (most common)
  - Iatrogenic CJD
  - Variant CJD
  - Familial
- Sporadic CJD
  - Age: - 5th – 7th decade
  - Rapidly progressive dementia
- ± Ataxia
- ± Extrapyramidal symptoms
- ± Visual symptoms
- ± Myoclonus
- Investigations
  - Clinical history
  - MRI
  - EEG
  - CSF study
- MRI – T_2 flair

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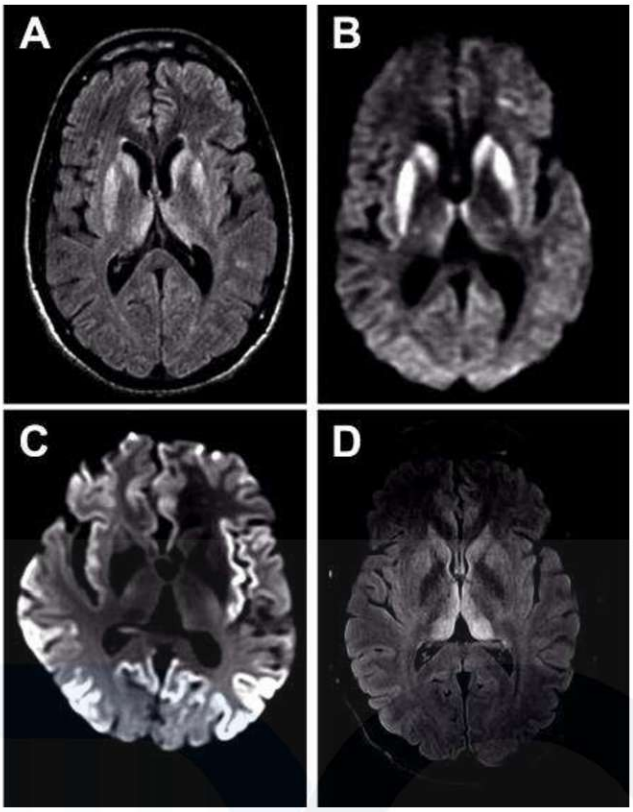

Fig: 1

- Cortical ribboning
- Hyperintensity of pulvinar nucleus

↓

Pulvinar sign/hockey stick sign

↓

More often in variant CJD

- EEG: - periodic sharp wave complexes with biphasic/triphasic morphology

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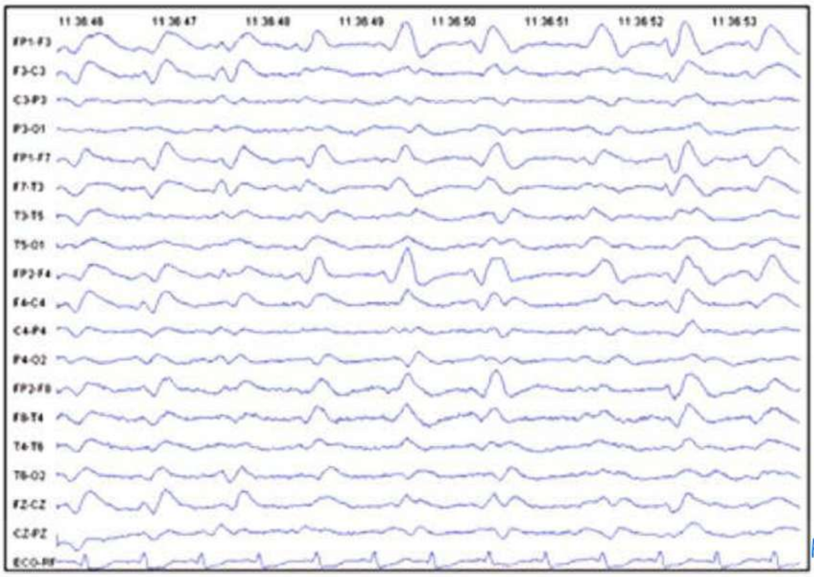

Fig: 2

- CSF study: -
  - Mildly elevated protein
  - CSF 14-3-3
  - S-100
  - Neuron specific enolase
- CSF RT – QUIC Study → specific
  - Real time quacking induced conversion
- Autopsy findings
  - Neuronal loss
  - Gliosis
  - Vacuolation (Spongiform change)

Variant CJD

- Younger age of onset
- Psychiatric symptoms

Iatrogenic CJD

- Contamination of EEG electrodes

- Contamination of Dural grafts
- Contamination of corneal transplant
- Growth hormone therapy
- Pituitary gonadotropin therapy

Familial CJD

- Mutation in PRNP gene

Treatment: - No definitive treatment.

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DELIRIUM

Introduction 00:00:38

- Acute onset confusional state with fluctuating cognition

Clinical Characteristics of Delirium
Acute onset of mental status change with fluctuating course
Attentional deficits
Confusion or disorganized thinking
Altered level of consciousness
Perceptual disturbances
Disturbed sleep/wake cycle
Altered psychomotor activity
Disorientation and memory impairment
Other cognitive deficits
Behavioral and emotional abnormalities

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- Causes of delirium

Major Causes of Delirium	
Metabolic	Electrolytes: hypo/hypernatremia, hypo/hypercalcemia, hypo/hypermagnesemia hypo/hyperphosphatemia Endocrine: hypo/hyperthyroidism, hypo/hypercortisolism, hypo/hyperglycemia Cardiac encephalopathy, hepatic encephalopathy, uremic encephalopathy Hypoxia and hypercarbia Vitamin deficiencies: thiamine, vitamin B12, nicotinic acid, folic acid Toxic and industrial exposures: carbon monoxide, organic solvent, lead, manganese, mercury, carbon disulfide, heavy metals Porphyria
Toxic	Intoxication and overdose Withdrawal: alcohol, benzodiazepines, barbiturates, amphetamines, cocaine, coffee, phencyclidine, hallucinogens, inhalants. meperidine, and other narcotics Drugs: anticholinergic, benzodiazepines, opiates, antihistamines, antiepileptics, muscle relaxants, dopamine agonists, monoamine oxidase inhibitors, levodopa, corticosteroids, fluoroquinolone and cephalosporin antibiotics, beta-blockers, digitals, lithium,
Infectious	Urinary tract infection, pneumonia, sepsis, meningitis, encephalitis

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Neurologic	Vascular: ischemic stroke, intracerebral or subarachnoid hemorrhagic , vasculitis Neoplastic: brain tumors, carcinomatous meningitis, paraneoplastic limbic encephalitis Seizure-related: postictal state, nonconvulsive status epilepticus Trauma: concussion, subdural hematoma.

- Endocrine – Hashimoto's encephalopathy

↓

Known as STREAT – steroid responsive encephalopathy autoimmune thyroiditis

Wernicke's encephalopathy 00:08:04

- Occurs due to thiamine deficiency
- Seen in chronic alcoholism
- Causes: -
  - Prolonged starvation
  - Anorexia nervosa
  - Prolonged i.v dietary supplementation
  - Hyperemesis gravidarum
- Clinical features: -
  - Confusion
  - Ophthalmoplegia
  - Ataxia
  - Nystagmus

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- Investigations: - MRI Brain
  - Axial T2 flair sequence

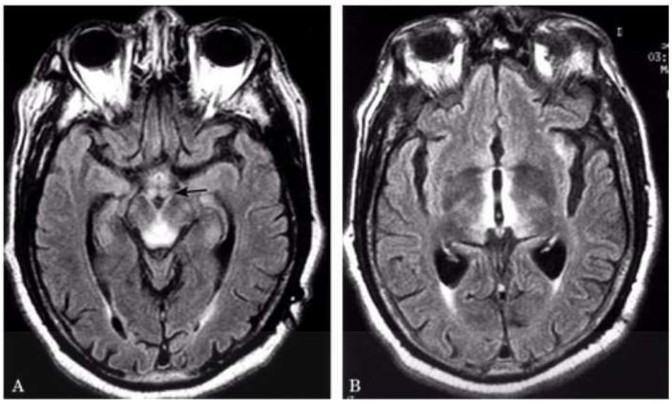

Fig: 1

  - Damage occurs predominantly in
    - Mamillary body
    - Dorsomedial thalamus
    - Periaqueductal grey mater
  - May also involve cerebellum
- Because of low sensitivity and low specificity, serum thiamine estimation not done
- RBC transketolase levels decreased
- Treatment: -
  - IV thiamine → 500mg 8th hourly → 100mg 8th hourly
  - Dextrose
- Recurrent attacks of encephalopathy results in Korsakoff syndrome
  - Unable to form new memories
  - Confabulation
- Memory problem is due to involvement of dorsomedial thalamus

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Neurological Complications Associated with Alcohol Abuse
Nutritional deficiency
Wernicke encephalopathy
korsakoff syndrome
Pellagra
Direct effects of alcohol
Acute intoxication
Fetal alcohol syndrome
Abnormalities of serum electrolytes and osmolality
Central pontine myelinolysis
Alcohol withdrawal
Withdrawal seizures
Alcoholic hallucinosis
Delirium tremens
Diseases of uncertain pathogenesis
Alcoholic neuropathy
Alcoholic myopathy
Amblyopia
Cerebellar degeneration
Marchiafava - bignami disease

Marchiafava – Bignami disease

- 40 years
- Chronic alcoholics
- Demyelination in central part of corpus callosum
- Acute confusional state/dementia

Pellagra

- Occurs due to niacin deficiency
- 3 D's
  - Dementia
  - Diarrhea
  - Dermatitis (casal's necklace).

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MULTIPLE SCLEROSIS AND OTHER CNS DEMYELINATING DISORDERS

Myelin disorders

- Dysmyelinating
  - ↓ Eg: Leukodystrophies
- Demyelinating
  - CNS
    - ↓ Multiple sclerosis
    - NMOSD
  - PNS
    - ↓ GBS
    - CIDP

Multiple sclerosis 00:02:36

- Sclerosis basically means area of hardening
- Autoimmune disorder of CNS characterised by
  - Inflammation → Predominantly chronic inflammatory
  - Demyelination
  - Scarring
  - Neuronal loss

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Epidemiology, risk factors & Etiopathogenesis 00:05:48

- Usually seen in regions far away from equator
- F>M 3:1
- Age group: 20-40years

Risk factors

- Combination of Genetic, environmental, host → Factors

Genetic factors

- HLADR2 and DR4

  ↓

  HLA DRBI 1501

  ↓

  Strongest genetic contribution
- Obesity
- Smoking
- EBV infection
- Vitamin D deficiency

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Pathogenesis

- Normally brain is a immune privileged site
- There is a breach in blood brain barrier

  ↓

  Inflammatory cells would gain access to the brain parenchyma and destroy the myelin
- Initially there is microglial activation

  ↓

  Secrete cytokines that stimulates astrocytes

  ↓

  VEGF produced makes blood brain barrier leaky

  ↓

  T cells and B cells gain access to immune site

  ↓

  Myelin destruction

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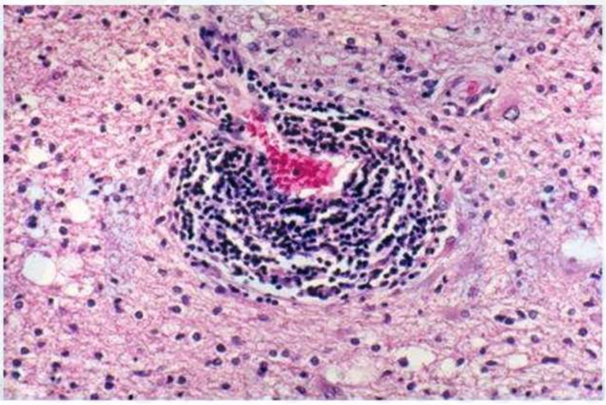
- Previously it was thought it is a T cell disease
- But B cells also are important for pathogenesis
- TH1 cells cause abnormal immune response
- TH17 cells also cause abnormal immune response
- Abnormal immune response is against myelin basic protein
- B cells → Help to moderate T cell response

  → Produce antibody against MOG

  (Myelin oligodendrocyte glycoprotein)
- In multiple sclerosis there is localised Ig production and oligoclonal antibodies are present in CSF (Oligoclonal antibodies)



" Perivascular cuffing " Fig: 1

- In early stage of disease there may be axonal damage also

Physiological changes 00:18:53

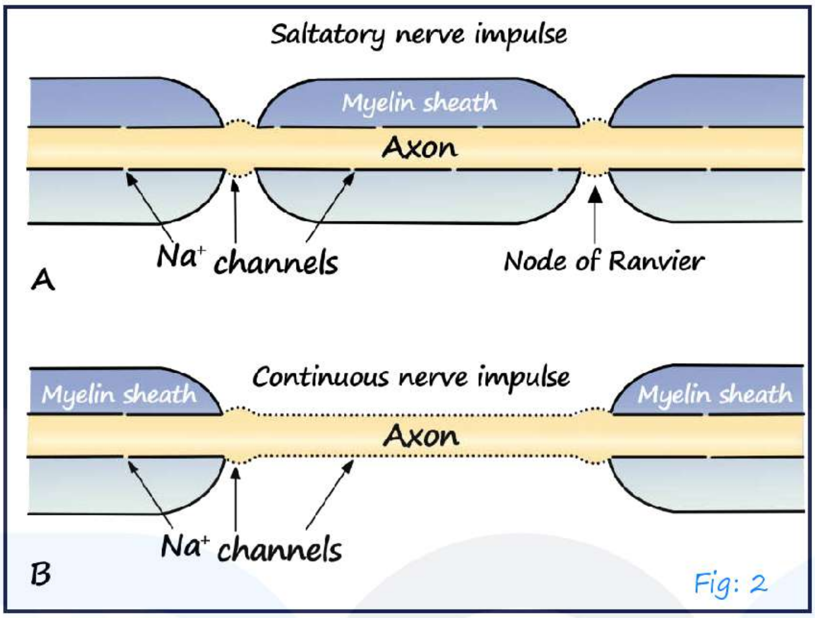


Fig: 2

A – (N)

B – MS

- When myelin is intact flow of information is by saltatory conduction → Impulses would jump from one node of Ranvier to another
- When myelin is damaged this saltatory conduction will not happen there will be continuous propagation of nerve impulses → Slower conduction

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Risk of developing multiple sclerosis (MS)	
1 in 3	If an identical twin has MS
1 in 15	If a fraternal twin has MS
1 in 25	If a sibling has MS
1 in 50	If a parent or half – sibling has MS
1 in 100	If a first cousin has MS
1 in 1000	If a spouse has MS
1 in 1000	If no one in the family has MS

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Clinical features 00:22:09

1. Sensory loss
   - Most common
   - Positive – Paraesthesia
   - Negative – Numbness
2. Optic neuritis
   - Painful unilateral visual loss
   - Not very severe
   - Pain on extra ocular movements
   - Decrease in visual acuity
   - Color desaturation
   - RAPD
3. Motor symptoms
   - Paraplegia
   - Hemiplegia
4. Bladder: 90% cases have bladder symptoms
5. Gaze: Internuclear ophthalmoplegia

   Damage to medial longitudinal fasciculus

   Ipsilateral adduction is impaired C/L eye abduction nystagmus

   - Young patient with internuclear ophthalmoplegia

     ↓

     Multiple sclerosis
   - Elderly patient with internuclear ophthalmoplegia → Stroke
   - Bilateral INO can occur in multiple sclerosis "Wall eyed eye INO" also known as WEBINO

- Pendular nystagmus (+)

6.Paroxysmal symptoms

- Lhermitte -Electric shock like pain radiating down the back over on flexion
- Occurs due to mechanosensitive of posterior column
- Intermittent tonic spasms
- Trigeminal neuralgia
- Glossopharyngeal neuralgia
- Hemifacial neuralgia
- Glossopharyngeal neuralgia
- Hemifacial spasm
- Facial myokymia
- Uthoff symptom – Heat sensitivity → After Exercise, hot shower → Further slowing of conduction velocity → AP propagation

7.Rare manifestations

- Facial palsy
- Cognitive dysfunction
- Depression

Clinical subtypes of multiple sclerosis 00:36:17

- Relapsing/Bout onset MS (Most common) 90%
- Primary progressive MS
- Secondary progressive MS

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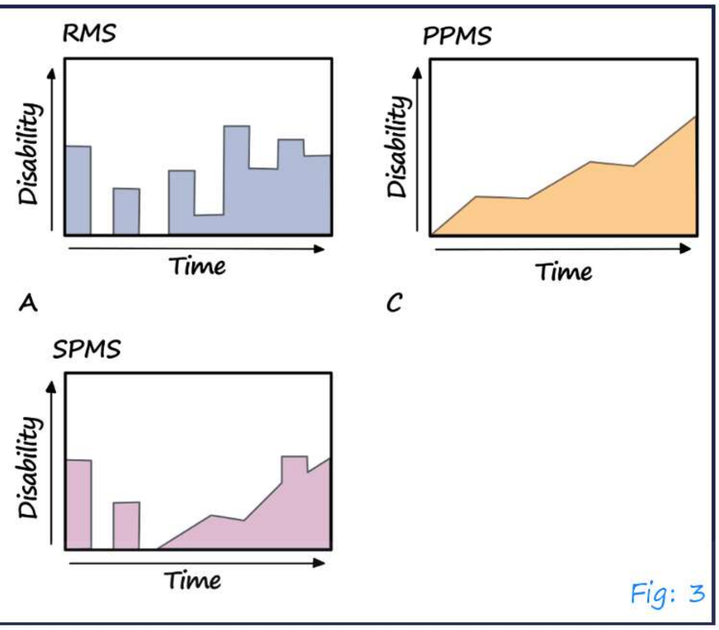

Fig: 3

1.Relapsing MS

- Patients would be having discrete clinical episodes from which there would be complete improvement

2.Primary progressive MS

- Disease progresses from beginning which means the patient has got disability followed by base line

3.Secondary progressive MS

- Initial 2 episodes is almost like RRMS and subsequently occurs disability and has progressive course

Diagnosis 00:40:11

1.MRI brain + Spinal cord with contrast

- Classical sites
  - Juxtacortical/Cortical
  - Periventricular
  - Infratentorial

- Spinal cord

- Lesions are hyper intense in T2 and T2 flair
- Acute lesions are contrast enhancing
- After 4-6weeks – No contrast enhancement

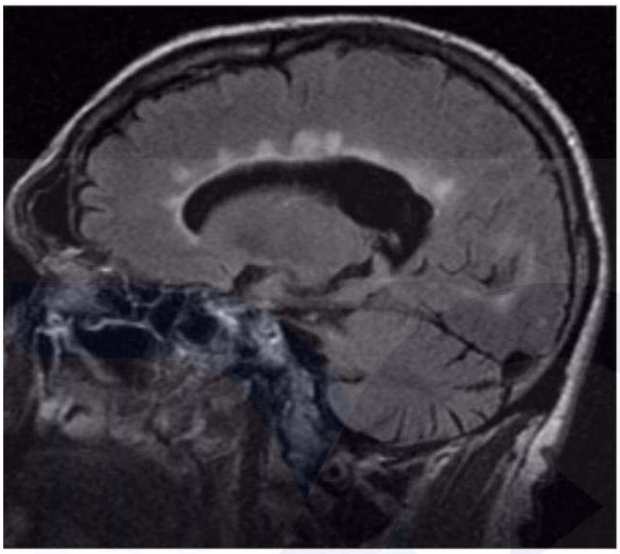

Fig: 4

- Hyperintensity perpendicular to corpus callosum

  ↓

  Dawson's fingers
- These lesions will be disseminated in time and space
- DIT: Dissemination in time means the lesions have occurred at different point of time (Old & new)
- DIS: Dissemination in space means more than 1 classical site should be involved

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Diagnosis criteria of multiple sclerosis

- Q. Most common Mc Donald 2017 criteria

Number of clinical attacks	Number of lesions with objective clinical evidence	Additional date needed for a diagnosis of multiple sclerosis
≥2	≥2	None
≥2	1 (As well as clear cut historical evidence of a previous attack involving a lesion in a distinct anatomic location)	None
≥2	1	Dissemination in space demonstrated by an additional clinical attack implicating a different central nervous system site or by MRI
1	≥2	Dissemination in time demonstrated by an additional clinical attack or by MRI or demonstration of CSF-specific oligoclonal bands

1	1	Dissemination in space demonstrated by an additional clinical attack implicating a different central nervous system site or by MRI And Dissemination in time demonstrated by an additional clinical attack or by MRI or demonstration of CSF-specific oligoclonal bands

2.VEP – Visual evoked potential

- Prolonged distal latency in optic neuritis

3.Role of CSF

- Demonstration of oligoclonal bands (OCB)

↓

Intraepithelial Ig synthesis

- 80% cases → positive OCB
- 2 or more OCB in CSF with relative absence in serum
- 2017 criteria → OCB positive → Proxy of DIT
- Clinically isolated syndrome: Only oligoclonal bands are present and no other lesions
- Sometimes clinically isolated syndrome may in due cause progress to multiple sclerosis
- Other than OCB, rest of CSF is normal
- Cells >75 → Not multiple sclerosis

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Treatment 01:01:41

i. Acute episode

ii. Disease modifying therapy

Acute episode

- Usually managed with steroids

↓

IV methylprednisolone 1gm IV OD x 5days

- Fulminant multiple sclerosis not responding to steroids

↓

Plasma exchange

Disease modifying agents

Injectables

- Interferon – beta – first agent to be approved by FDA
- Glatiramer acetate – Polypeptide containing amino acids
- Both have modest efficacy

Oral

- Fingolimod → First agent made available
- Dimethyl fumarate
- Teriflunomide

Monoclonal antibodies

- Alemtuzumab
- Ocrelizumab
- Natalizumab → Associated with progressive multifocal leukoencephalopathy

Newer agents

- Sipolimod
- Cladribine

Treatment strategies

- Induction ↓ More chance of side effects
- Escalation ↓ Currently preferred strategy
  Starts with modest efficacy drugs

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- Primary progressive MS – FDA approved – Ocrelizumab (Anti CD20)
- Secondary progressive MS – FDA approved – Siponimod & Cladribine

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Multiple sclerosis in pregnancy 01:15:10

- Pregnancy – Immune tolerant state
- In 2nd & 3rd trimester – multiple sclerosis is in quiescent stage
- There is a chance of relapse postpartum
- Active disease – Disease modifying therapy
- Teriflunomide: Category x drug extensive hepatobiliary reabsorption
- Can persistent in circulation even after 2years of stoppage of drug
- Wash out can be done with activated charcoal
- Preferred drugs → Category B – Glatiramer acetate

  Category C – Interferon Beta

Variants of multiple sclerosis 01:19:15

- Fulminant multiple sclerosis

  "Marburg variant"
- Tumefactive MS

  "Tumor like lesions"

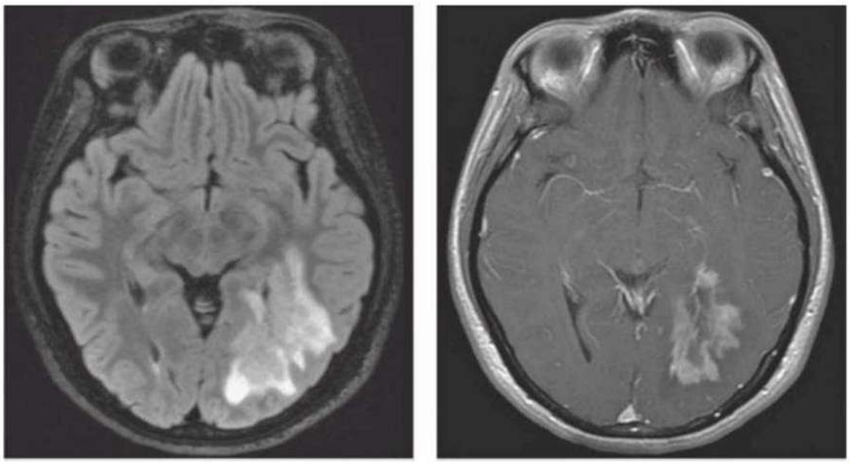

Fig: 5

- Balo's concentric sclerosis

  "Alternate rings of demyelination and remyelination"

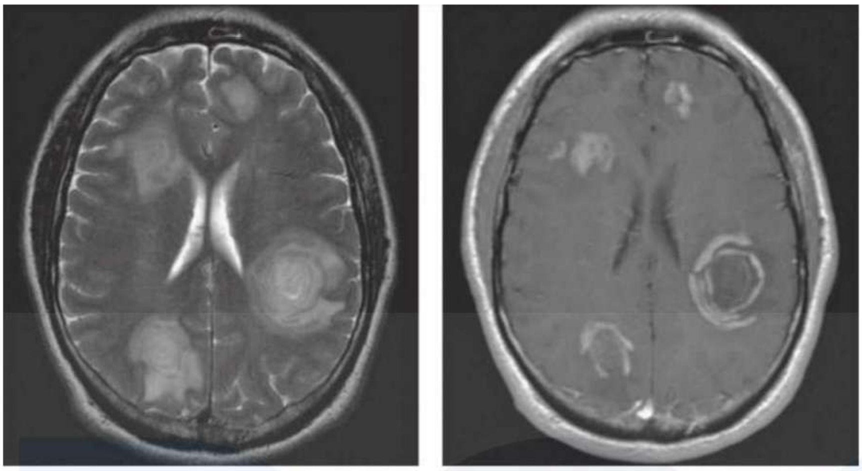

Fig: 6

- These have Poor prognosis compared to typical MS

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NMO SPECTRUM DISORDERS

Introduction 00:01:20

- Asian population → Opticospinal MS
- Neuromyelitis optica/Devic's disease
- In 2004, specific causative antibody was found

  ↓

  Anti AQ P_4 (aquaporin 4)
- 1999 – Wingerchuck criteria
- 2006 – Revised wingerchuck criteria
- 2007 – NMOSD

80% positive AQP4 → Astrocytopathy

20% negative AQP4 → ¼th anti MOG (Myelin Oligo-dendrocyte Glycoprotein) → Oligodendrocyte

- AQP4 – located in foot processes of astrocytes & nodes of ranvier
- 2015 – IPND

  International panel for NMO diagnosis

AQP_4 IgG Disease 00:07:04

- F > M
- Predilection for Asian and African population

Core clinical characteristics

i. Optic neuritis: B/L and severe, >50% length of ON
Optic chiasma may be involved

ii. Transverse myelitis – LETM
(Longitudinally extensive Transverse myelitis)
↓
Length of demyelination $\geq$ 3 vertebral segments

iii. Area postrema syndrome: -
- Intractable nausea, vomiting

iv. Symptomatic cerebral syndrome – SIADH

v. Symptomatic diencephalic syndrome – Narcolepsy

vi. Acute Brainstem syndrome

- 40% associated with autoimmune disorder
  - SLE
  - Sjogren's
  - APLA
- Rarely → Paraneoplastic manifestations

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Investigations –

1. MRI Brain + Spinal cord with contrast

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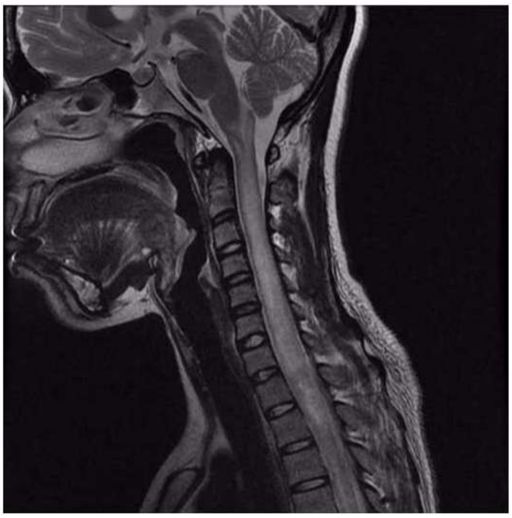

Fig: 1

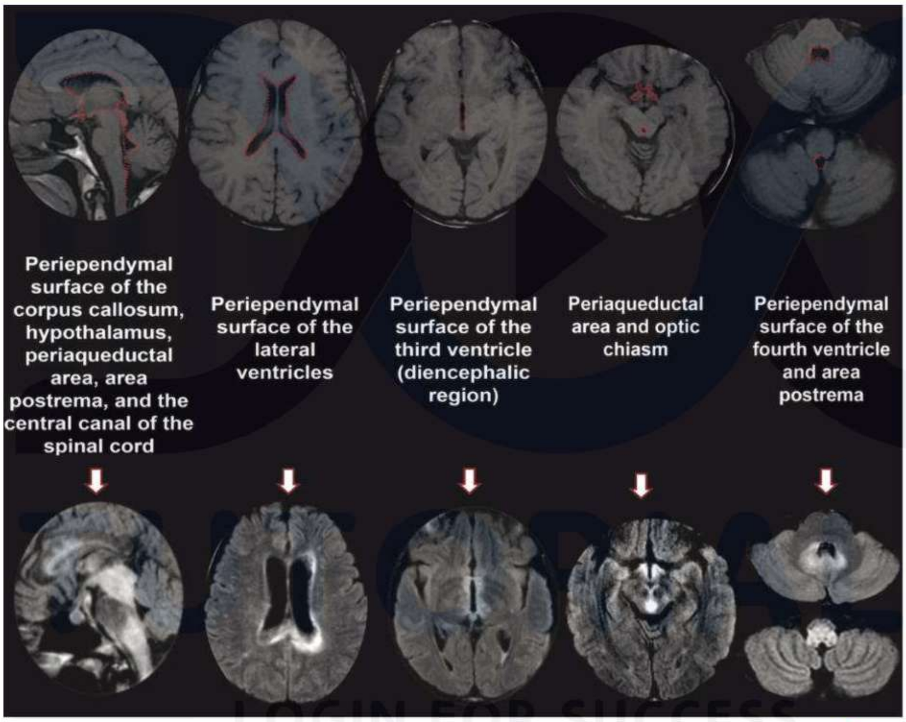

Fig: 2

- AQP4 concentrated in circumventricular region

- More aggressive disease
- No progression

2.Serum AQP4 antibody

3.CSF – Pleocytosis

10-15% have OCB

MOG IgG disease 00:18:44

- Common in middle age, may involve children
- H/O antecedent infection
- Optic neuritis - >50%

  Optic disc edema

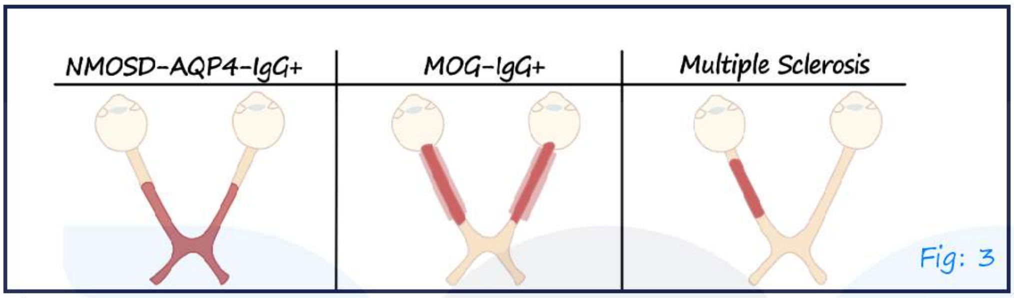

Fig: 3

AQ4 IgG	MOG – IgG+	Multiple sclerosis
↓	↓	↓
>50%	>50%	<50%
Posterior inv.	Anterior invol.	Middle
	Disc edmea	

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- Conus medullaris involvement ⊕
- Clinically similar to ADEM (Acute Disseminated Encephalomyelitis)
- Diagnosis – Antibody testing

  Cell based assay

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Treatment of NMOSD

- Acute: – IV methyl prednisolone pulse therapy

  1gm IV once daily * 5 days

  +

  Plasma exchange

- Maintenance: – Azathioprine

  Mycophenolate mofetil

  Rituximab (anti CD20)

- Newer Treatment: – Eculizumab (C5 complement Inhibitor)

  Inebilizumab (anti CD19)

  Tocilizumab (anti IL-6R)

  Satralizumab (anti IL-6R)

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ADEM

Introduction 00:00:30

- Acute disseminated encephalomyelitis
- CNS demyelinating disease
- Characterized by multifocal demyelination involving grey and white matter
- Age: - children

Etiology 00:01:50

Etiology

Post vaccinal

→Aberrant immune response

- Old generation rabies vaccine
- Measles vaccines

Post infectious

- Mumps
- Rubella
- Influenza
- Para influenza
- HIV
- Dengue
- Zika
- Chicken pox-high chance of cerebellar involvement

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Clinical features 00:04:22

- Clinical features: -

  i. Prodromal phase: -

  - Fever

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- Headache
- myalgia

ii. Full blown ADEM

- Fever
- Encephalopathy
- Seizures
- Quadriparesis
- Paraparesis
- B/L optic neuritis

Investigation 00:05:42

- INVESTIGATION: -
  - MRI brain with contrast – large fluffy lesions involving grey matter and white matter, lesions are contrast enhancing
  - CSF study: - lymphocytic pleocytosis and moderately elevated protein count
  - VEP: - increased distal latency

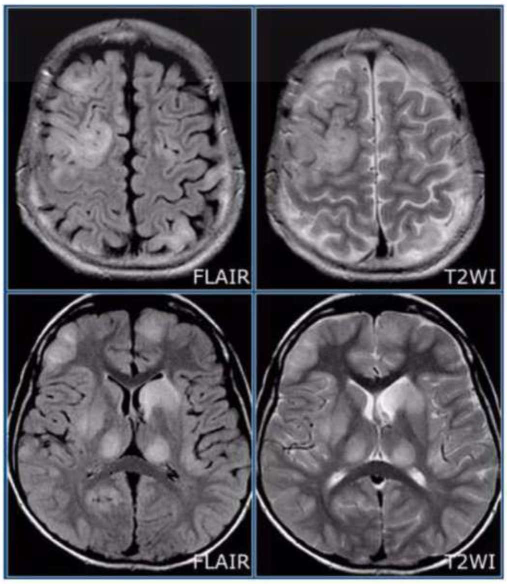

Fig: 1

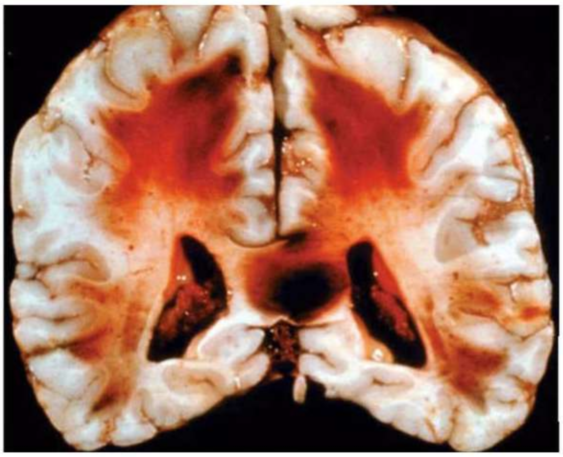

Fig: 2

Hurst disease – Acute hemorrhagic leukoencephalitis

↓

Lots of necrosis and hemorrhage

Treatment 00:09:30

- Treatment of ADEM
  - Acute: – I.V Methyl prednisolone 1 gm IV OD x 5 days

    +

    Plasma exchange/IV Ig
  - ADEM is Monophasic illness
  - Multiphasic ADEM
  - MOG IgG disease – ADEM like presentation.

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ATAXIAS

Ataxias 00:00:54

- Greek word "a taxis" – without order
- Impaired coordination of voluntary motor activity
- Possible sites of lesion
  - Cerebellum or it's connections
  - Large fibres of peripheral nerves
  - Dorsal root ganglion
  - Posterior column
  - Frontal lobe and its connections
  - Vestibular system
- Cerebellum is connected to
  - Midbrain – Superior cerebellar peduncle
  - Pons – Middle cerebellar peduncle
  - Medulla – Inferior cerebellar peduncle

Cerebellum 00:06:05

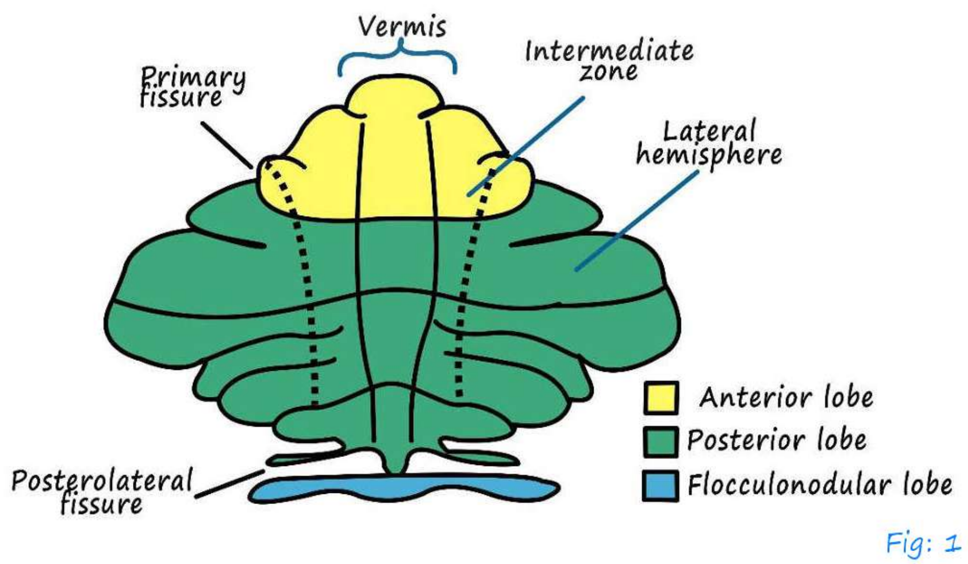

Fig: 1

- Primary fissure separates anterior lobe from posterior lobe
- Posterolateral fissure separates posterior lobe from flocculonodular lobe

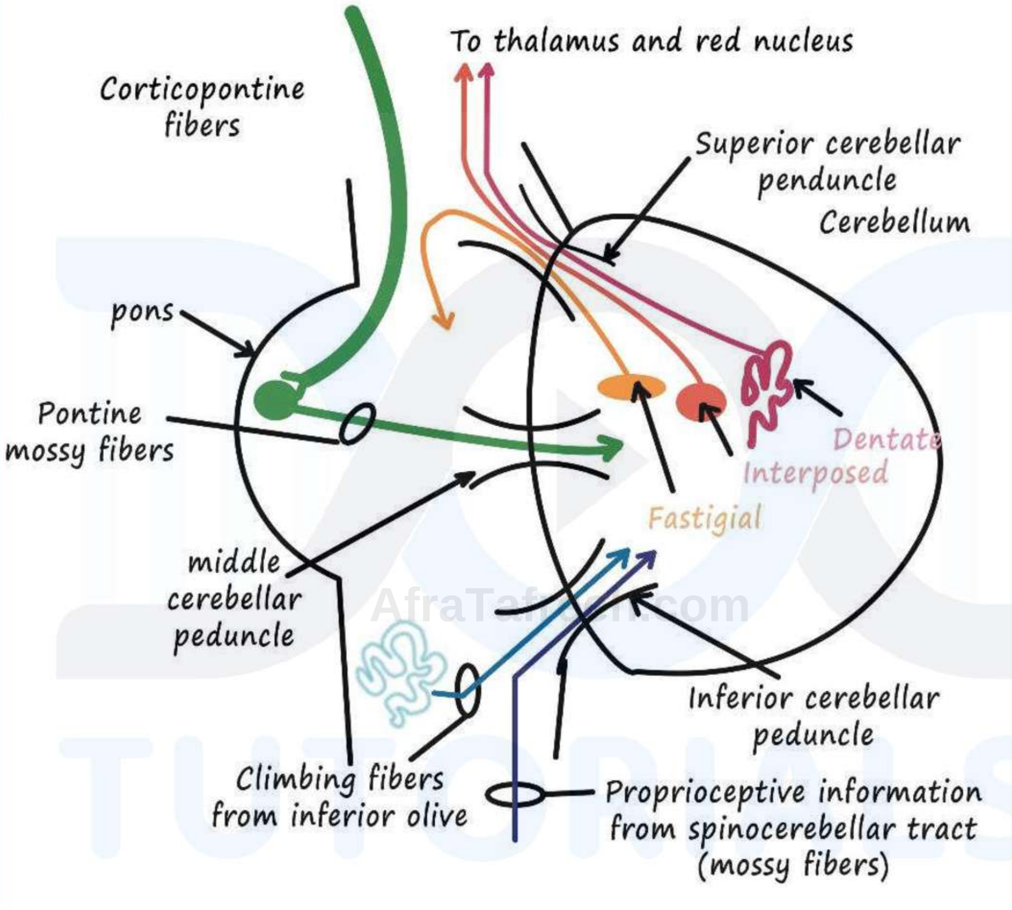

Fig: 2

- Dentatorubrothalamic tract goes via superior cerebellar peduncle

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Functional divisions of cerebellum

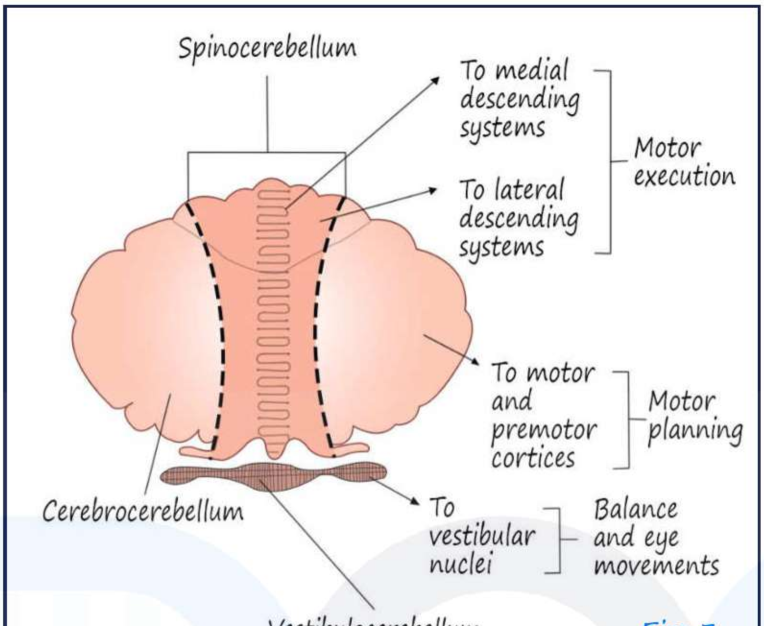

Fig: 3

- Cerebellum is important for rate, range and direction of movement

Cerebellar lesion features 00:10:07

- Ataxia
  - Limb ataxia
  - Gait ataxia / Truncal ataxia (vermis)
- Dysarthria
  - Staccato speech → Undue stress on syllables
  - Scanning speech → Undue separation on syllables
- Titubation (head hooding)
- Tremor (Intention)
- Nystagmus (Gaze evoked)

Cerebellar ataxia 00:14:36

- Etiology → Acute, Subacute, Chronic

Acute causes of cerebellar ataxia

- Vascular causes: ischemic or hemorrhagic cerebellar strokes
- Ethanol intoxication
- Toxins (mercury, thallium, toluene, solvents)
- Medication (phenytoin, carbamazepine, phenobarbital, lithium)
- Multiple sclerosis
- Meningitis, particularly basilar meningitis
- Viral cerebellitis
- Cerebellar abscess
- Wernicke encephalopathy/ thiamine deficiency

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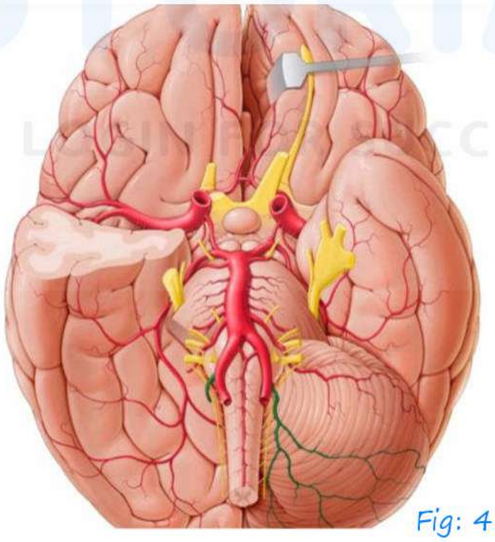

Fig: 4

- So, whenever you have vascular insult either ischemic or haemorrhagic stroke, these vessels are involved

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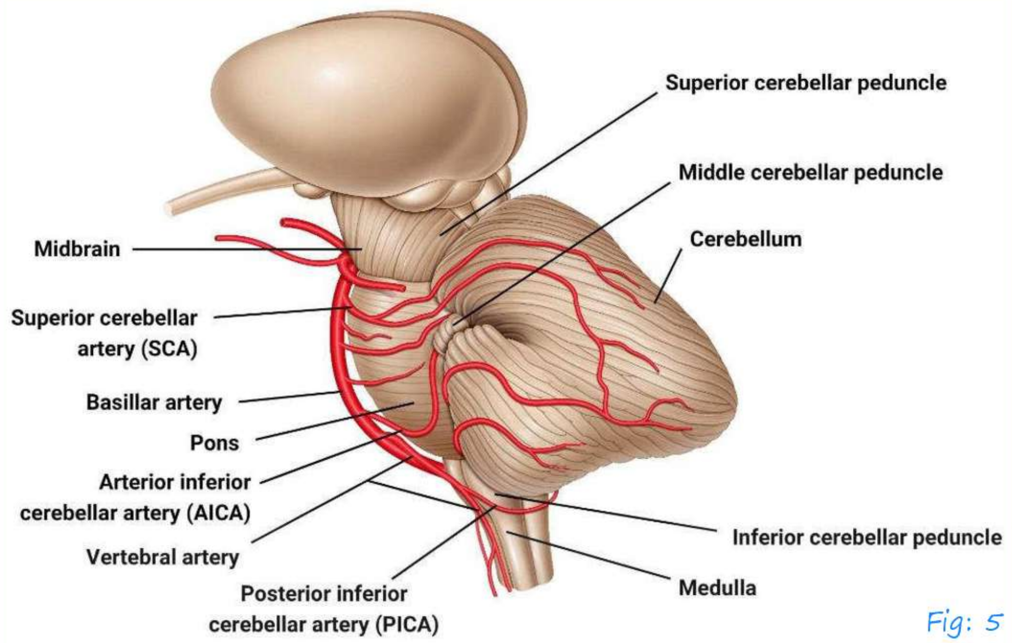

Fig: 5

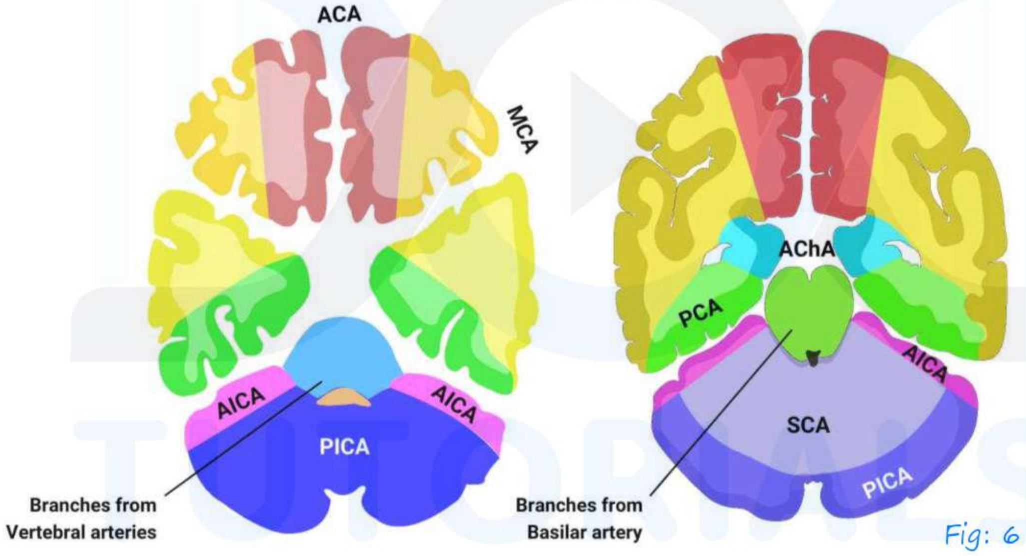

Fig: 6

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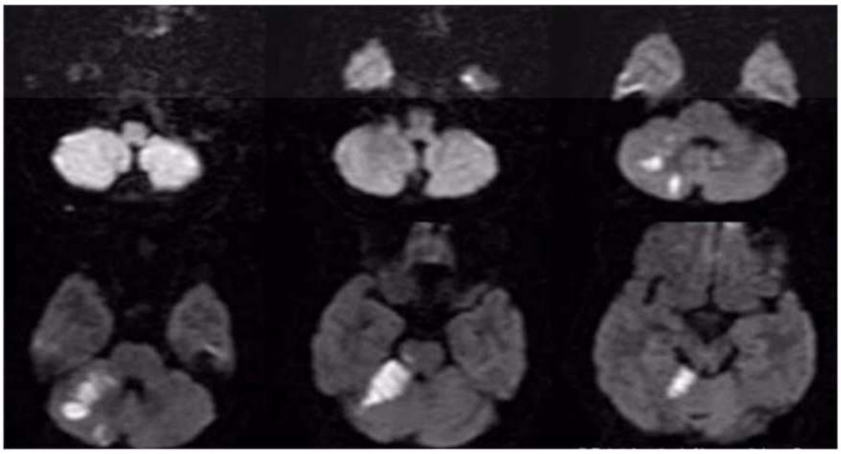

Fig: 7

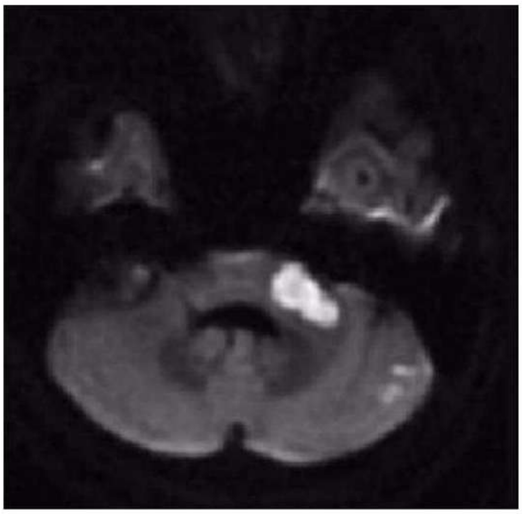

Fig: 8

- Deafness due to involvement of labyrinthine artery

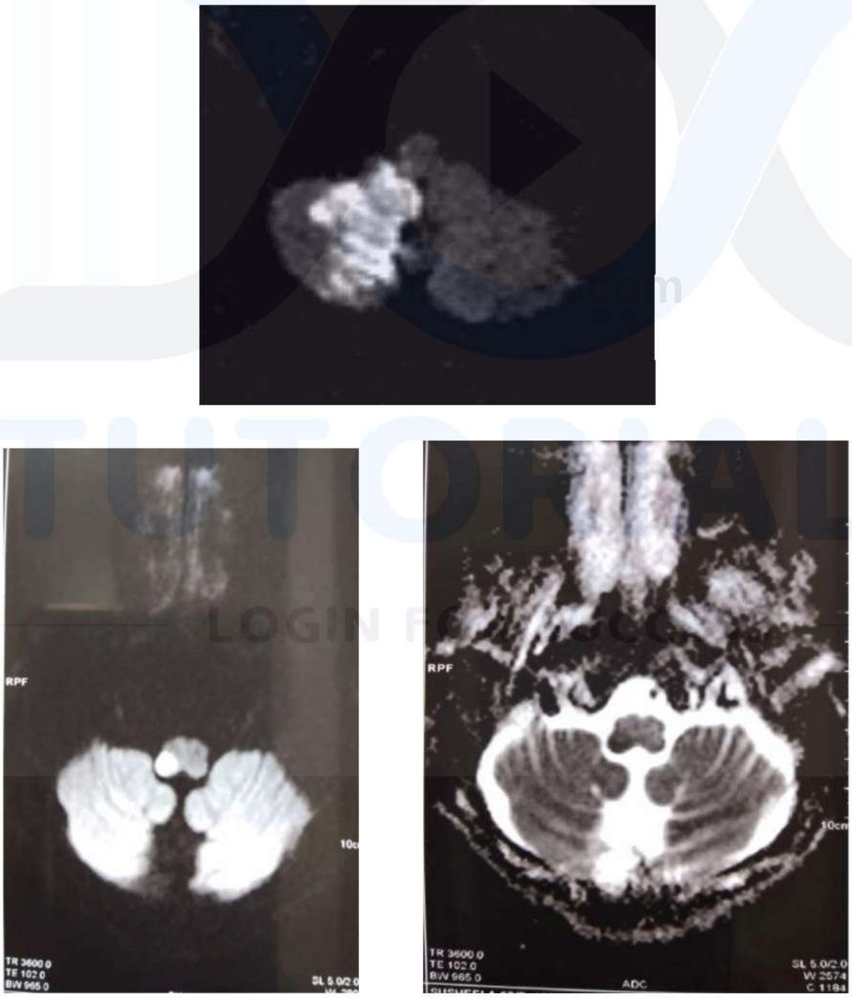

Fig: 9

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- DWI – (R) PICA stroke
- DWI ⎤ → lateral medullary syndrome
- ADC ⎦ ↓

Vertebral artery involved

Subacute causes of cerebellar ataxia (weeks to months)

- Paraneoplastic cerebellar Degeneration
- Brain tumours
- Creutzfeldt Jacob disease
- Superficial siderosis
- Anti-glutamic acid decarboxylase ataxia
- Superficial siderosis → Trauma causing SAH
  → Hemosiderin deposition in subpial region

Chronic causes of cerebellar ataxia (months to years)

- Ataxia associated with gluten sensitivity
- Genetic ataxia
- Mitochondrial disease
- Multiple system atrophy
- Idiopathic late onset cerebellar ataxia
- Most common – Genetic ataxia

Genetic ataxia

- May have different patterns of inheritance

  AD | AR | X-Linked

Autosomal dominant ataxias

- Spinocerebellar ataxias (SCA)
- Episodic ataxias
- Dentatorubropallido luysian atrophy

SCA

- Heterogenous group
- Ranging from 1 → 40
- Most of them are repeat expansion disorders
- Most common type of SCA world – SCA-3 (Machado joseph disease)
- SCA – 6 is predominantly cerebellar
- Others will have combination of ataxia +

  Q. Most common type of SCA in India – SCA – 2

  Q. Type of SCA associated with
- Others will have combination of ataxia +

  Pyramidal +

  Extrapyramidal +

  Peripheral neuropathy

  Q. Most common type of SCA in India – SCA – 2

  Q. Type of SCA associated with retinitis pigmentosa – SCA – 7

  Q. SCA – 2,3,1,6 → CAG repeat expansion
- Normally CAG produces glutamine on repeat expansions it produces polyglutamine → Toxic to neuron and produces cell death

  Q. SCA – 8 – Untranslated CTG repeat expansion

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Q. SCA-10 – Pentanucleotide repeat expansion disorder

Q. SCA – 12 – Untranslated CGA repeat expansion disorder

- Chronic progressive symmetric ataxia (+)

  Pyramidal

  Extrapyramidal

  Peripheral neuropathy

  Family history

  ↓

  diagnosis → SCA

Friedrich's ataxia 00:42:37

- Q. most common hereditary ataxia
- AR
- Mutation in frataxin gene on chromosome

  ↓

  GAA repeat expansion

- Frataxin – Important for iron homeostasis in mitochondria
- Because of frataxin mutation
- Mitochondrial dysfunction
- Order of neurodegeneration –
- Q. Dorsal root ganglion
- Spinal cord
- Peripheral nerves

Clinical features

- Age <25years
- Differential diagnosis – Ataxia telangiectasia (1st decade)
- Ataxia
- Extension plantar response
- Ankle jerk absent
- Spasticity
- Nystagmus
- Cardiomyopathy
- Arrhythmias
- Diabetes
- Scoliosis
- Pes cavus
- Treatment: Idebenone

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Fig: 10

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Episodic causes of cerebellar ataxia

- Genetic episodic ataxia
- **Psychogenic ataxia**
- **Mitochondrial disease**
- **Multiple sclerosis**

Approach to ataxia

- History
- **Is it a pure ataxic syndrome or ataxia +?**
- Parkinsonism – MSA-c
- Dementia - CID
- Myoclonus -CID
- Vision problems and ocular motor disturbances – MFS, MS, Vit B12 def, Wernicke's
- Peripheral neuropathy
- Fever – infectious cerebelli tees
- GI symptoms – Whipple's, Abetalipoproteinemia
- Constitutional symptoms – paraneoplastic
- Multisystem – mitochondrial
- **Focused approach can help narrow differentials**

Miller fischer syndrome

- Ataxia
- Areflexia
- Ophthalmoplegia
- Is there any drug history?
  - Alcohol

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- Phenytoin, carbamazepine, levetiracetam
- Lithium
- Anti-cancer drugs (5-FU, cytosine arabinoside)

- Is there any history of heavy metal exposure? (Lead, mercury, bismuth)
- History of high-risk sexual behaviour? (HIV)
- History of trauma
- History of thyroid dysfunction?
- History of jaundice –(Wilson's disease)
- Alcohol per se damage purkinje cells
- Is there any family history
- Draw the family tree (ideally 3 generations are a must)
- Pattern of inheritance
- Autosomal dominant
- Autosomal recessive
- X linked
- Mitochondrial

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Examination

- focused head to foot examination based on available information

  Telangiectasia

  Pes cavus

  KF ring

  CVJ anomaly (neck length ratio)

  Short 4th metatarsal

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- Short 4th metatarsal → Refsum's disease

Neurological Examination

- Speech
- Eyes
- Limbs
- Gait
- Eyes: Gaze evoked nystagmus

  Saccades → Hypometric/Hypermetric

  Pursuit → Broken pursuit

  Down beat nystagmus

Lab Investigations – Based On Clinical Judgement

- Routine blood investigations
- Peripheral smear
- CSF study
- Vitamin B1, B12, E levels
- Anti-TPO
- Anti-GAD, anti-TTG, anti-gliadin
- Retro
- Paraneoplastic panel
- Imaging

ALS AND OTHER MOTOR NEURON DISEASES

Amyotrophic lateral sclerosis 00:00:56

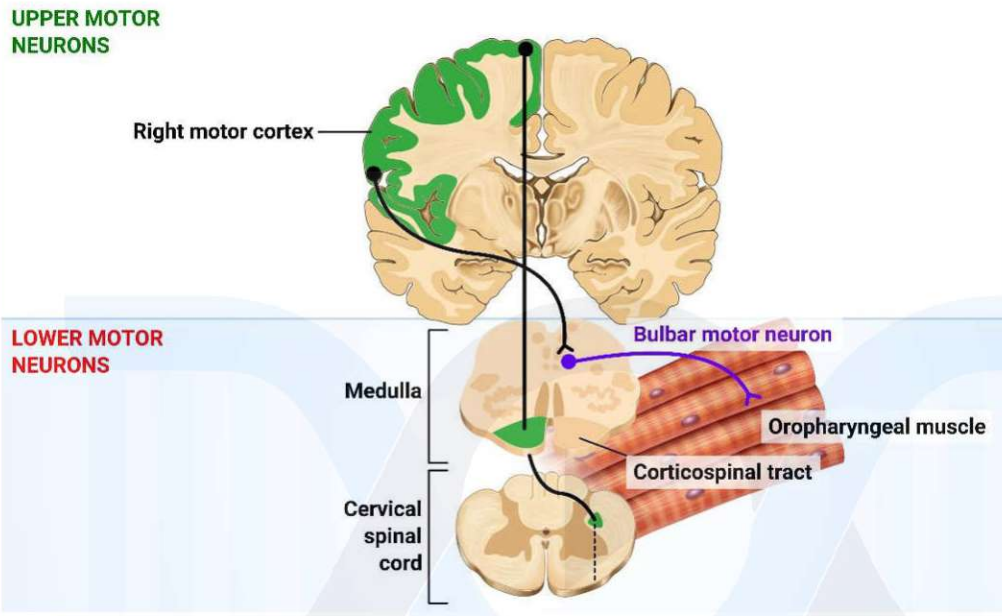

Fig: 1

- UMN – origin from layer V of cerebral cortex
  - corticospinal tract
  - corticobulbar tract→ supplies brain stem
- LMN – somatic motor neuron
  - Bulbar motor neuron

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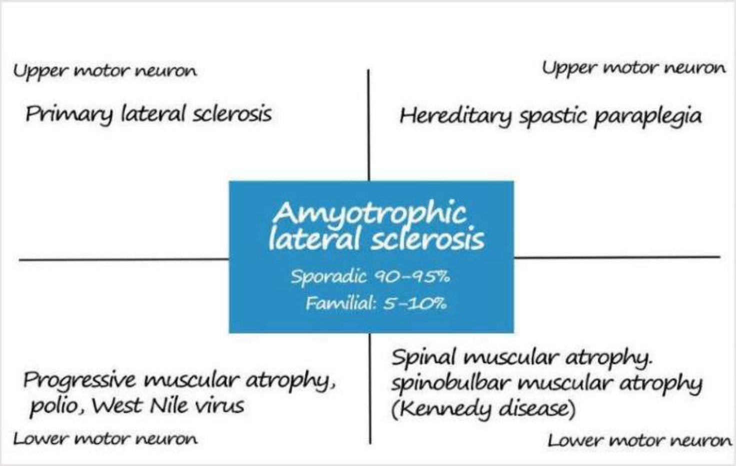
D/B UMN & LMN 00:04:49

Sign	Upper motor neuron	Lower motor neuron
Atrophy	Non	Severe
Fasciculations	None	Common
Tone	Spastic	Decreased
Distribution of weakness	Pyramidal / regional	Distal / segmental
Muscle stretch reflexes	Hypractive	Hypoactive / absent
Baninski sign	Present	Absent

- Fasciculations → muscles twitching occurring in single motor unit

Diseases of motor neurons 00:10:28



The spectrum of motor neuron diseases.

- Most common motor neuron disease – amyotrophic lateral sclerosis

↓

Affects UMN & LMN

Sporadic Motor Neuron Diseases	
CHRONIC	ENTITY
Upper and lower motor neuron Predominantly upper motor neuron Predominantly lower motor neuron	Amyotrophic lateral sclerosis Primary lateral sclerosis Multifocal motor neuropathy with conduction block Motor neuropathy with paraproteinemia or cancer Motor predominant peripheralneuropathies
Other	
Associated with other neurodegenerative disorders Secondary motor neuron disorders	
Acute	
Poliomyelitis Herpes zoster Coxsackie virus West Nile virus	

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- MMN LB → due to anti GM1 antibodies
  → Responds well to Iv Ig

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Disorders of Upper Motor Neurons and Their Key Characteristics	
Disorders	**Key characteristics**
Primary lateral sclerosis	A diagnosis of exclusion
Hereditary spastic paraplegia	Heredity, usually autosomal dominant, spastin gene mutation, other mutations (see text), "sporadic"
HTLV-1-associated myelopathy	Slowly progressive myelopathy, endemic, and positive HTLV-1
HTLV-2-associated myelopathy	Amerindian, IV drug abuser, concomitant HIV
Adrenomyeloneuropathy	X-linked recessive inheritance, adrenal dysfunction, myelopathy, very long-chain fatty acid assay
Lathyrism	History of consumption of chickling peas
Konzo	Eastern African, cassava root consumption

Amyotrophic lateral sclerosis 00:22:32

- Neurodegenerative disease
- Involves UMN & LMN
- 90 -95 % - sporadic, 5- 10 % familial

Currently Known Genes Responsible for Familial Forms of Amyotrophic Lateral Sclerosis and Their Protein Product	
Gene	**Protein**
SOD1	Superoxide dismutase (Cu/Zn)
C9orf72	Uncharacterized
FUS	Fused in sarcoma
TARDBP	TDP-43
ALS2	Alsin
ANG	Angiogenin
SETX	Senataxin
VAPB	Vesicle-associated protein B
UBQLN2	Ubiquilin

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m/c gene mutation – c9 or f72

- Clinical features
  - 5-6th decades
  - Pure motor system disease
  - Asymmetric weakness→ progressive
  - Degeneration of neurons either due to Glutamate
  - Mediated excitotoxic or free radical injury

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- Usually begins upper extremities
- When lower extremities involved, m/c – symptom ↓ Cramps
- Bulbar involvement → problems in chewing, swallowing
  → Nasal regurgitation
  → Nasal twang
- Corticobulbar involvement → spinal dysarthria
  → emotional incontinence

  or

  Pseudobulbar palsy
- A motor neuron involved → wasting
  → denervation atrophy
  → fasciculations
- Life span 35 years

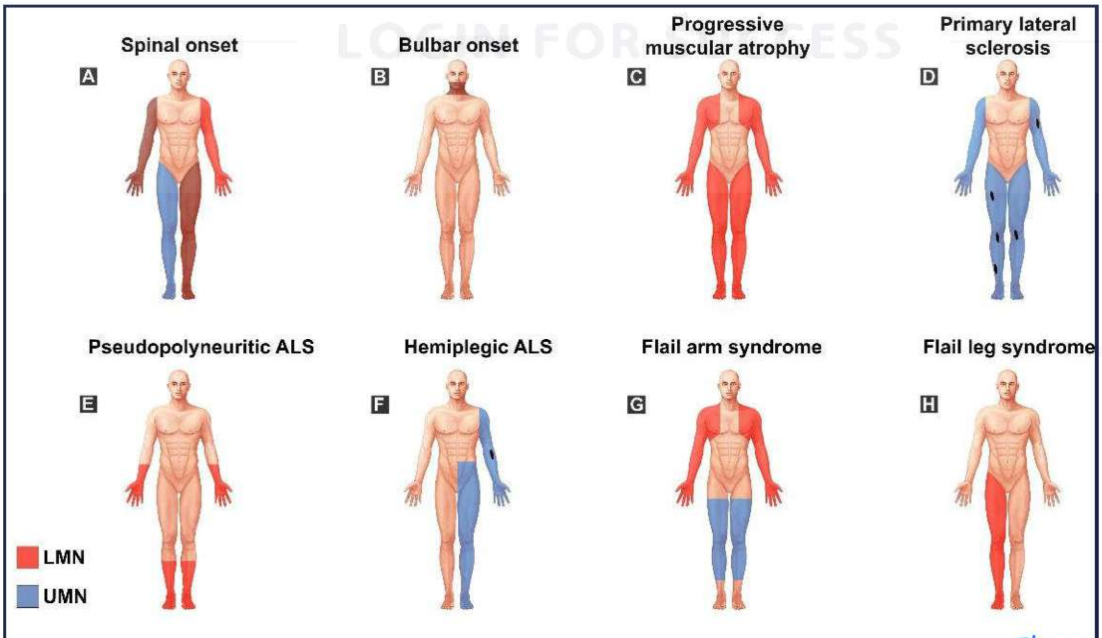

Fig: 2

D/b pseudobulbar 2 bulbar palsy

	Pseudobulbar palsy (b/1 UMN lesions V,IX, X, XII)	Bulbar palsy (b/1 LMN lesions V, IX, X, XII)
Speech	Spastic dysarthria (Donald Duck / Hot potato speech)	Nasal
Jaw jerk	Increase	Decrease
Gag reflex	Increase	Decrease
Tongue	Spastic	Wasted, fasciculations
Other	UMN signs in limbs Pseudobulbar affect (e.g. uncontrollable/ inappropriate laughter) More common	
Causes	B/L cerebrovascular disease (commonest); MS; MND	MND; GBS; MG

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Fig: 3

- Split hand phenomenon -thenar muscles more affected than
  Hypothenar muscles

→Dropped head syndrome

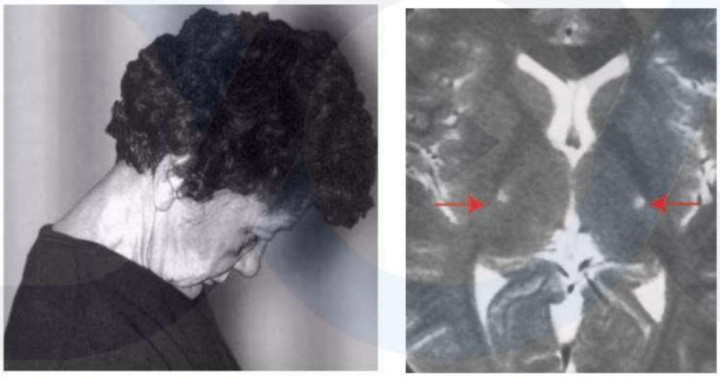
Fig: 4

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- Diagnosis: - clinical feature

  +

  Electrodiagnosis study (NCS+EMG)

  - NCS → Decrease amplitude in motor conduction study
  - EMG → active →fibrillation potentials
    Positive sharp waves
    Fasciculations
    Large amplitude long duration polyphasic

Motor unit action potential

(MUAP)

- 2 criteria – El Escorial criteria

Awaji shima criteria

- Treatment: - No definitive treatment

FDA approved: - i. Riluzole

↓

Inhibited glutamate

Mediated excitotoxicity

ii. Edaravone

↓

Free radical scavenger

- Supportive care
- Pseudobulbar symptoms → Dextromethorphan + Quinidine

Etiology of Motor Neuron disease

Etiology of Motor Neuron Disorders	
Diagnostic category	**Investigation**
Structural lesions Parasagittal or foramen magnum tumors Cervical spondylosis Chiari malformation of syrinx Spinal cord arteriovenous malformation	MRI scan of head (including foramen magnum and cervical spine)
Infections Bacterial-tetanus, Lyme Viral-poliomyelitis, herpes zoster Retroviral-myelopathy	CSF exam, culture Lyme titer Anti-viral antibody HTLV-1 titers

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Intoxications, physical agents Toxins-lead, aluminum, others Drugs-strychnine, phenytoin Electric short, x-irradiation	24-h urine for heavy metals Serum lead level
Immunologic mechanisms Plasma cell dyscrasias Autoimmune polyradiculopathy Motor neuropathy with conduction block Paraneoplastic Paracarcinomatous	Complete blood count Sedimentation rate Total protein Anti-GM1 antibodies Anti-Hu antibody MRI scan, bone marrow biopsy
Metabolic Hypoglycemia Hyperparathyroidism	Fasting blood sugar Routine chemistries including calcium
hyperthyroism deficiency of folate,vitamin B_{12}, vitamin E malabsorption deficiency of copper, zinc mitochondrial dysfunction	PTH thyroid function[a] vitamin B_{12}, vitamin E, folate a serum zinc, copper [a] 24-h stool fat, carotene, prothrombin time fasting lactate, pyruvate, ammonia consider mtDNA
hyperlipidemia	lipid electrophoresis
hyperglycinemia	urine and serum amino acids CSF amino acids
hereditary disorders c9orf72 superoxide dismutase TDP43 FUS/TLS androgen receptor defect (Kennedy's disease)	WBC DNA for mutational analysis

Spinal muscular atrophy (SMA) 00:53:22

Childhood and Adult Spinal Muscular Atrophies					
SMA type	Age at onset	Maximum function achieved	Survival/prognosis	Inheritance	Defective gene
0. Prenatal	Prenatal	Needs respirator support at birth	Fatal at birth without respirator support	AR	SMN gene
1. Infantile SMA (Werdnig-Hoffmann)	Birth to 6mo	Sits with support	Death by age 2yr	AR	SMN gene
2. Intermediate SMA	After 18mo	Sits independently	No walking. adulthood	AR	SMN gene
3. Juvenile (Kugelberg Welander)	Before 18mo	Walks independently approx. 25 steps	Adulthood	AR	SMN gene
4. Adult-onset SMA (pseudo myopathic SMA)	After 5 y (most >30 y)	Walks normally	Slow progression Proximal or distal	AR, AD "Sporadic	SMN gene VAPB, dynactin unknown, distal overlap with HMN-V

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- Due to SMN gene – Survival Motor Neuron

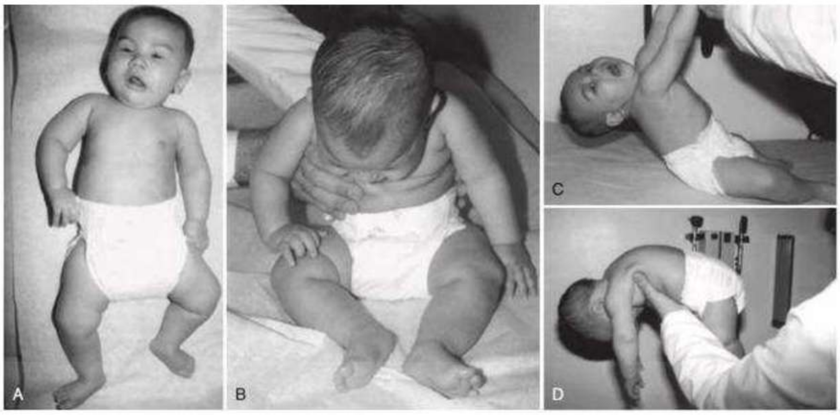

Fig: 5

Kennedy's diseases 00:58:43

- Also referred to as x- linked bulbospinal neuropathy

Characteristic Features of Kennedy Disease
Pathogenesis: X-linked recessive inheritance Abnormal CAG expansion in the gene encoding androgen receptor protein Neurological manifestations: Slowly progressive limb-girdle muscle weakness Early tremor Slowly progressive moderate bulbar dysfunction Muscle cramps and prominent fasciculations Facial fasciculations Systemic manifestations: Gynecomastia (60%-90%)

Endocrine abnormalities (testicular atrophy, feminization, infertility)

Diabetes mellitus

Laboratory studies:

Markedly abnormal sensory nerve conduction studies

Elevated serum creatine kinase

Abnormal sex hormone levels

Abnormal CAG repeats in the androgen receptor gene

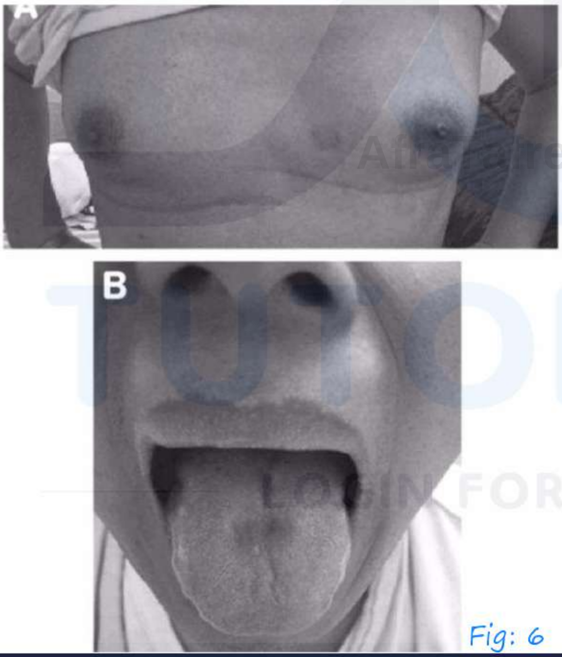

Fig: 6

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DISORDER OF PERIPHERAL NERVE

Lower Motor Neuro 00:00:30

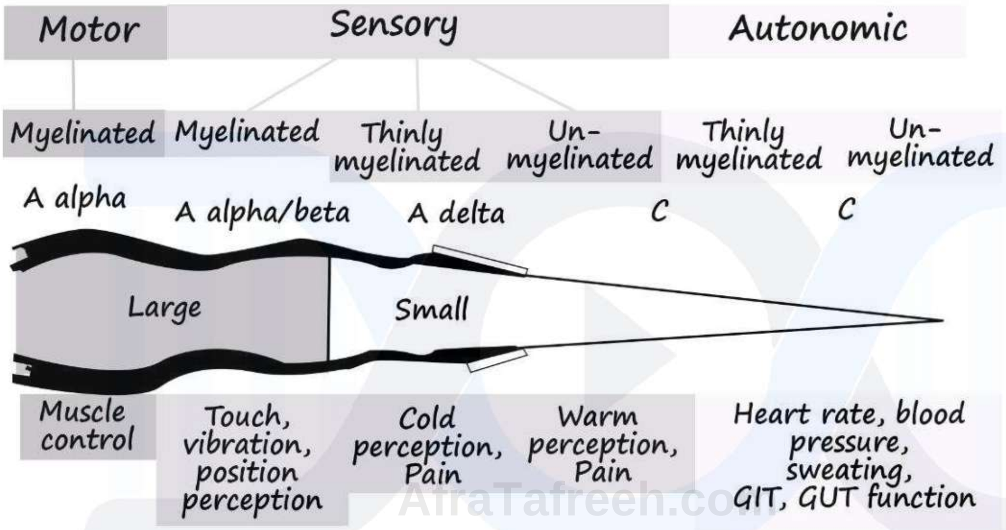
- Involves → Anterior horn cell.
- Roots
- Dorsal root ganglion
- Plexus
- Peripheral nerve
- NMJ
- Muscle
- Ganglion involved → Neuronopathy
- AHC involved → Motor neuronopathy
- DRG involved → Sensory neuronopathy (Ganglionopathy)

Classification 00:04:18

- Pathologic Classification of Neuropathic Disorders
- Neuronopathies (pure sensory or pure motor or autonomic):
- Sensory neuronopathies (ganglionopathies)
- Motor neuronopathies (motor neuron disease
- Autonomic neuropathies
- Peripheral neuropathies (usuay sensorimotor):
- Myelinopathies
- Axonopathies
- Large and small fiber

- Small fiber
- Aα, Aβ – Large myelinated fibers
- As – small myelinated fibers
- C- Unmyelinated fibers

Causes of sensory neuropathy 0:06:44



- Peripheral nerve consists of motor, sensory and autonomous part →
  Hence called mixed nerve
- Motor is carried by large myelinated fibers (Aα)
- Sensory can be → Large myelinated
  →Small
  →unmyelinated
- Large myelinated fibred carry → vibration
  → Joint position sense
  → Two-point discrimination

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Classification of Peripheral Nerve Disease
Mononeuropathy
Plexopathy
Brachial plexopathy
Lumbar plexopathy
Sacral plexopathy
Radiculopathy
Cervical radiculopathy Thoracic radiculopathy Lumbosacral radiculopathy
Multiple mononeuropathy (mononeuropathy multiplex)
Polyneuropathy
Symmetrical polyneuropathy
Asymmetrical polyneuropathy
Polyradiculoneuropathy

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Etiology of Neuropathic Disorders
I. ACQUIRED
Dysmetabolic states
Diabetes mellitus
Neuropathy related to renal disease
Vitamin deficiency states (ex. Vitamin B12 deficiency)
Primary amyloidosis
Immune-mediated
Guillain-Barre Syndrome
Chronic inflammatory demyelinating polyneuropathy (CIDP)
Vasculitis
Infectious
Herpes zoster
Leprosy, Lyme, HIV, and Sarcoid related
Cancer related
Lymphoma, myeloma, carcinoma related
Paraneoplastic subacute sensory neuronopathy
Drugs or toxins
Chemotheraphy induced
Other drugs
Heavy metals and industrial toxin
Mechanical/Compressive
Radiculopathy
Mononeuropathy
Unknown etiology
Cryptogenic sensory and sensorimotor neuropathy

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Amyotrophic lateral sclerosis

II. HEREDITARY

Hereditary Motor Sensory Neuropathy

(Charcot-Marie - Tooth disease)

Hereditary neuropathy with predisposition to pressure palsies

Familia! Brachial plexopathy

Familial amyloidosis

Porphyria

Other rare peripheral neuropathies

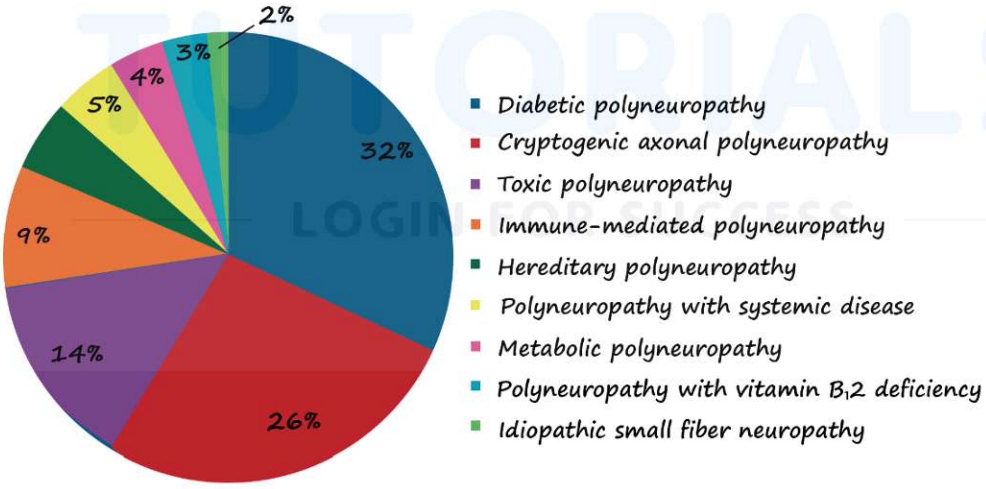
(Fabry's, metachromatic eukodystrophy,adrenolen kodystrophy, Refsum's disease etc.)

Motor neuron disease

Spinal muscular atrophy

Familial amyotrophic lateral sclerosis

X-linked bulbospinal muscular atrophy



Estimated prevalence of common polyneuropathy categories.

Neuropathy

Axonal — Demyelinating

Chronic axonal neuropathies
Drugs or toxins
-alcohol
- chemotherapeutic agents-for example, vincristine, cisplatinum
- organophosphate
- phenytoin
- antibiotics-for example, metronidazole, dapsone
- statins
Infections
- leprosy Borrelia
- HIV, HTLV1.
Connective tissue diseases
Sjogren's syndrome
systemic lupus erythematosus
rheumatoid arthritis
Metabolic
diabetes
Paraneoplastic
- lung, ovarian carcinoma
Inherited
- CMT 2 and X
- familial amyloid neuropathies
Vitamins -vitamin B12
- vitamin E
- pyridoxine toxicity
Endocrine
- hypothyroidism
Paraprotein
-lung, ovarian carcinoma
Inherited

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-CMT 2 and X

-familial amyloid neuropathies

Vitamins

-vitamin B1

-vitamin E

-pyridoxine toxicity

Endocrine

-hypothyroidism

Paraprotein

-myeloma

-Waldenstrom's disease

-benign monoclonal gammopathies

Demyelinating neuropathies

- Acute
  - Guillain Barre syndroje (GBS)
- Chronic
  - chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
  - paraproteinemia related amiodarone toxicity
  - Refsum's disease
  - Charcot-Marie-Tooth (CMT) types 1, X and AR CMT 1
  - metachromatic leucodystrophy
  - statins

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Approach to peripheral neuropathy 00:24:45

Approach to Neuropathic Disorders: Seven Key Questions
1. What systems are involved? • Motor, sensory, autonomic, or combinations 2. What is the distribution of weakness? Only distal versus proximal and distal • Focal/asymmetric versus symmetric 3. What is the nature of the sensory Involvement? • Temperature loss or burning or stabbing pain (e.g., small fiber) • Vibratory or proprioceptive loss (e.g., large fiber) 4. Is there evidence of upper motor neuron Involvement? • Without sensory loss . With sensory loss 5. What is the temporal evolution? • Acute (days to 4 weeks) Subacute (4-8 weeks) • Chronic (>8 weeks) • Monophasic, progressive, or relapsing-remitting 6. Is there evidence for a hereditary neuropathy? • Family history of neuropathy . Lack of sensory symptoms despite sensory signs 7. Are there any associated medical conditions? Cancer, diabetes mellitus, connective tissue disease or other autoimmune diseases, infection (e.g., HIV, Lyme disease, leprosy) Medications including overs the counter doing that may cause a toxic

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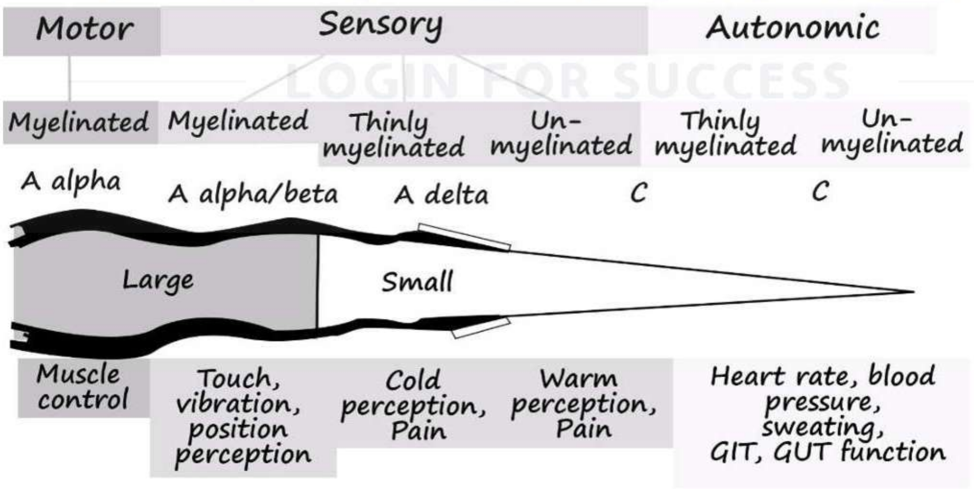
- Motor → weakness
- Sensory

Large fiber → Numbness, tingling, Pins& needles → Sensory ataxia

small fiber → burning

- Autonomic
  - orthostatic hypotension
  - palpitation
  - Bradycardia
  - constipation/Diarrhea
  - Erectile dysfunction
  - Bowel. Bladder dysfunction



Predominantly sensory neuropathies diabetes

- thiamine deficiency
- malignancy
- leprosy
- hereditary sensory neuropathies
- amyloid
- uraemia
- sarcoid

Neuropathies with Autonomic Nervous System Involvement
ACUTE Acute panautonomic neuropathy (autoimmune, paraneoplastic) Guillain-Barré syndrome Porphyria Toxic: vincristine, Vacor (rodenticide) **CHRONIC** Diabetes mellitus Amyloid neuropathy (familial and primary) Paraneoplastic sensory neuronopathy (malignant inflari matory sensory polyganglionopathy) Human immunodeficiency virus-related autonomic neuropathy Hereditary sensory and autonomic neuropath

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Neuropathic Disorders that Produce Asymmetric/Focal Weakness
Motor neuron disease
Amyotrophic lateral sclerosis
Radiculopathy-cervical or lumbosacral
Root compression from osteoarthritis
Root compression from herniated disc
Herpes zoster focal paresis (with rash)
Meningeal carcinomatosis and lymphomatosis
Sarcoid
Amyloid
Chronic immune sensory polyradiculopathy
Plexopathy-cervical, thoracic, or lumbosacral
Immune-mediated/Idiopathic
Neoplastic infiltration
Diabetic radiculoplexopathy (primarily lumbosacral)
Familial brachial plexopathy
Hereditary neuropathy with liability to pressure palsy
Mononeuropathy multiplex due to:
Vasculitis
Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM)
Multifocal motor neuropathy
Multifocal acquired motor axonopathy (MAMA)
Lyme disease
Sarcoid

Small-Fiber Neuropathies
Diabetes mellitus and impaired glucose tolerance
Amyloid neuropathy (early familial and primary)
HIV-associated distal sensory neuropathy
Hereditary sensory and autonomic neuropathies
Fabry disease
Tangier disease
Sjögren (sicca) syndrome
Cryptogenic small-fiber neuropathy

Large fiber Neuropathy → vit B12 deficiency
→ Friederichs ataxia
→ GB3
→ C1DP

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- Vit B12 deficiency

Hypocritic myelopathy
HIV
Vit E deficiency
] LMN+UMN involved

Some Causes of Polyradiculopathy
Structural
Spondyloarthropathy
Spinal stenosis
Radiation
Neoplastic
Non-Hodgkin lymphoma
Acute leukemia
Melanoma

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Carcinoma
Infectious
Lyme disease
Cytomegalovirus
Human immunodeficiency virus (HIV)
Tuberculosis
Herpes zoster
Schistosomiasis
Inflammatory
Sarcoidosis

Causes of Poly radiculomyelopathy
Hereditary
Porphyria
Inflammatory
Guillain-Barré syndrome
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome
Toxic
Arsenic
n-Hexane
Amiodarone
Diphtheria
Metabolic/Ischemic
Diabetic radiculoplexus neuropathy
Idiopathic
Idiopathic radiculoplexus neuropathy

Thenar atrophy in chronic bilateral carpal tunnel syndrome.

Fig: 1

Neuropathy

- Length dependent
- Length independent

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Axonal neuropathy

→ glove and stocking

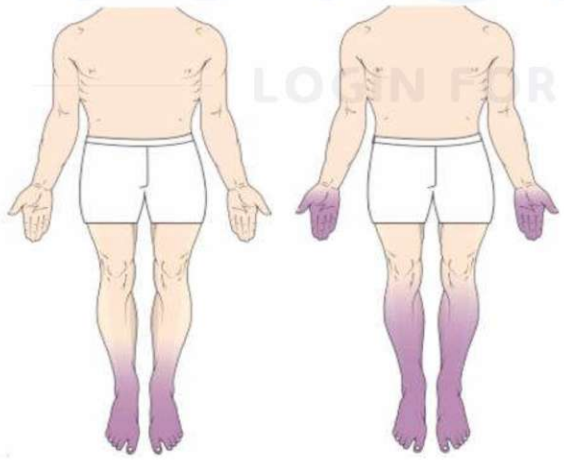

Fig: 2

→ length dependent polyneuropathy

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Common Causes of Length-dependent Polyneuropathy		
Category	Notable Examples	Estimated Prevalence of All Types
Diabetes mellitus	Large fiber sensory predominant small fiber Impaired glucose tolerance	33% 10-25% of above Unknown
Chronic idiopathic axonal polyneuropathy	Idiopathic	25 55%
Small fiber neuropathy	Idiopathic	2%
Hereditary	Charcot-Marie-Tooth disease (hereditary motor sensory neuropathy), hereditary sensory and autonomic neuropathy, hereditary motor neuropathy	5-33%
Metabolic	Vitamin B_1/other nutritional deficiency, end organ failure/critical illness polyneuropathy	12%
Toxic	Chemotherapy, industrial environmental toxins	14%
Inflammatory	Distal acquired demyelinating symmetric neuropathy associated with IgM monoclonal protein	9%

Neuropathies with Facial Nerve Involvement
Guillain-Barré syndrome
Lyme disease
Sarcoidosis
Chronic inflammatory demyelinating polyradiculoneuropathy (rare)
Human immunodeficiency virus 1 infection
Gelsolin familial amyloid neuropathy (Finnish)
Tangier disease

Polyneuropathies with Predominantly Upper-Limb Motor Involvement
Multifocal motor neuropathy
Lewis-Sumner variant of CIDP
Lead neuropathy*
Porphyria
Tangier disease
Familial amyloid neuropathy type 2
Hereditary motor neuropathy (uncommon forms)
*Frequently presents with wrist drop.

Neuropathies with Skin, Nail, or Hair Manifestations	
Disease	Skin, nail, or hair manifestations
Vasculitis	Purpura, livedo reticularis
Cryoglobulinemia	Purpura
Fabry disease	Angiokeratomas

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Leprosy	Skin hypopigmentation
Osteosclerotic myeloma (POEMS syndrome)	Skin hyperpigmentation
Variegate porphyria	Bullous lesions
Refsum disease	Ichthyosis
Arsenic or thallium intoxication	Mees lines
Thallium poisoning	Alopecia
Giant axonal neuropathy	Curled hair
POEMS, Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.	

Hereditary neuropathies 01:03:34

- m/c – chariot Marie tooth disease 9LMT)
- Young
- Positive family history
- Slowly progressive neuropathy

Chariot Maxie tooth disease 01:04:47

- Also referred Hereditary Motor Sensory neuropathy (HMNS)
- Subtypes
- CMT – I → most common (CMt-10)→ PMP 22 duplications

  2

  3

  4

  X

CLASSIFICATION OF CMT

- CMT1
  - AD - Predominantly demyelinating - Uniform conduction velocity slowing (<38 m/s)
- CMT2
  - AD- Predominantly axonal
  - Relatively normal velocities
  - Prom 12% htly reduced SNAP or CMAP
- CMT3
  - AD- severe demyelination - Infancy
- CMT4
  - AR- demyelinating
- CMTX
  - XL - Axonal

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Clinical Presentation

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CMT 1A CLINICAL PRESENTATION

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- Age group: 1st - 3rd decade
- Distal predominant weakness
- Lower limb predominant weakness
- Sensory signs >>> Sensory symptoms

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Inverted champagne bottle Appearance

Fig: 3

→ Onion bulb formation

↓

Due to demyelination 2 remyelination

↓

Thickened nerves

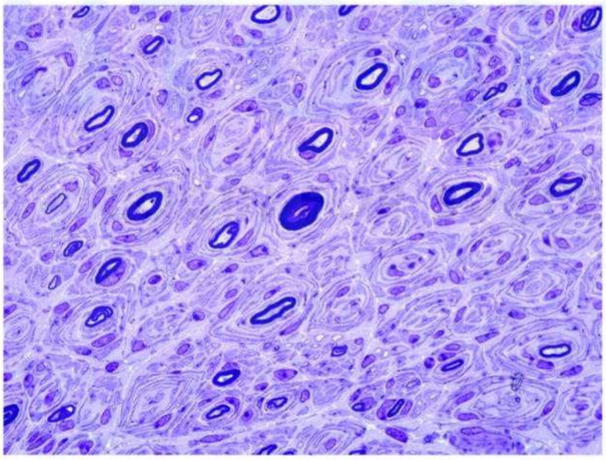

Fig: 4

HNPP 00:15:21

- Hereditary neuropathy with liability to pressure palsies
- Ad

- HASN– Hereditary sensory and autonomic neuropathy
- Hereditary Neuralgic amyotrophy

Rare Hereditary Neuropathies
Hereditary Disorders of Lipid Metabolism
Metachromatic leukodystrophy Krabbe's disease (globoid cell leukodystrophy Fabry's disease Adrenoleukodystrophy/adrenomyeloneuropathy Refsum's disease Tangier disease Cerebrotendinous xanthomatosis
Hereditary Ataxias with Neuropathy
Friedreich's ataxia Vitamin E deficiency Spinocerebellar ataxia Abetali poproteinemia (Bassen Korrzweig disease)
Disorders of Defective DNA Repair
Ataxia telangiectasia Cockayne's syndrome
Glant Axonal Neuropathy
Porphyria
Acute intermittent porphyria (AIP) Hereditary coproporphyria (HCP) Variegate porphyria (VP)
Familial Amylold Polyneuropathy (FAP)
Transthyretin related Gelsolin related Apolipoprotein A1 related

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Fabry's disease

- Due to α galactosidase A
- Painful acroparesthesia
- Cornea verticillate
- Vortex keratopathy
- Whorl like deposits
- Adrenoleukodystrophy / Adreno myeloneuropathy

↓

Peroxisomal ABC gene

Refsum's disease

- Phytanoyl CoA hydroxylase
- Cerebellar ataxia
- Retinitis pigmentosa
- CSF protein increased
- Short 4th metatarsal

Acquired neuropathy 01:23:11

- Diabetes mellites

Classification of Diabetic Neuropathies
GENERALIZED SYMMETRICAL POLYNEUROPATHIES
Distal sensory or sensorimotor polyneuropathy
Small-fiber neuropathy
Autonomic neuropathy

Large-fiber sensory neuropathy
FOCAL AND ASYMMETRICAL NEUROPATHIES
Cranial neuropathy. (Single or multiple)
Truncal neuropathy thoracic radiculopathy)
Limb mononeuropathy (single or multiple)
Lumbosacral radiculoplexopathy (amyotrophy, proximal neuropathy)
COMBINATIONS
Polyradiculoneuropathy Diabetic neuropathic cachexia

- Pain
- Asymmetry
- Wasting
- Wasting

(Asymmetry, Wasting, Wasting: Bruns Garland syndrome)

Amyloidosis

- Walden Strom's macroglobulinemia
- Multiple myeloma
- Lymphoma
- Small fiber neuropathy
- May cause automatic disinfection also

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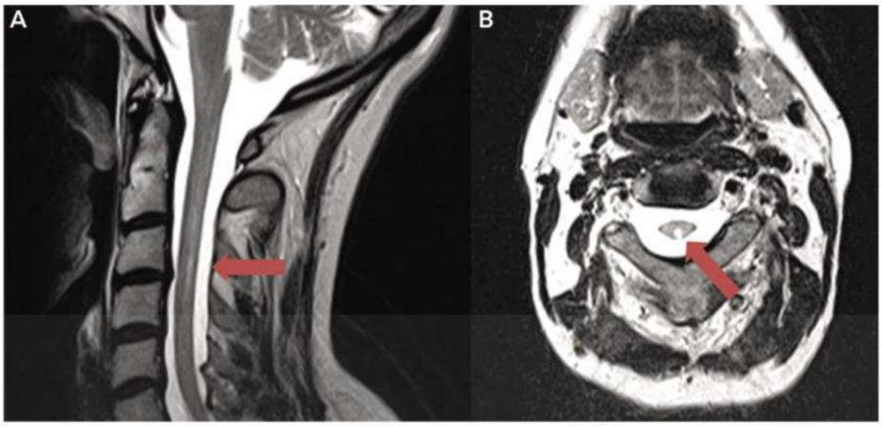
Vitamins and Minerals Commonly Implicated in Nutrient-deficiency Neuropathy			
Vitamin or Mineral	**Associated Condition**	**Nerve Fiber Type**	**Notes**
Cobalamin (vitamin B12)	Strict vegetarian diet, pernicious anemia, gastritis, inflammatory bowel disease, bariatric surgery, metformin, proton pump inhibitors	Large fiber sensory, myeloneuropathy	Corticospinal tract signs, cognitive impairment, macrocytic anemia
Folate	Inflammatory bowel disease, bariatric surgery, methotrexate, phenytoi	Large fiber sensory	May coexist with cobalamin deficiency, macrocytic anemia
Copper	Malnutrition, zinc toxicity, iatric surgery	Large fiber sensory, myeloneuropathy	Corticospinal tract signs, macrocytic anemia, neutropenia
Thiamine (vitamin B_1)	Alcoholism, malnutrition, bariatric surgery, malabsorption	Large fiber sensorimotor, polyradiculoneuropathy	Wernicke encephalopathy/ Korsakoff syndrome; serum measurement may not be reliable indicator
Pyridoxine (vitamin B6)	Isoniazid, alcoholism, bariatric surgery, malabsorption	Small fiber sensory more than large fiber sensory and motor involvement	Excess causes sensory ganglionopathy
α-Tocopherol (vitamin E)	Lipid malabsorption, bariatric surgery, genetic	Large fiber sensory	Notes

Tremor, cerebellar signs, myopathy



Inverted 'V' sign →SACD Fig: 5

Summary of infectious neuropathies		
Agent	**Type**	**Notes**
Mycobacterium leprae (leprosy)	Mononeuropathy multiplex, sensory neuropathy	Predilection for cool body regions such as extremities and face
Borrelia burgdorferi (Lyme disease)	Sensorimotor polyneuropathy, mononeuritis multiplex, radiculopathy	Neurologic manifestations can occur at acute and latent stages
Human immunodeficiency virus (HIV)	Axonal polyneuropathy. mononeuritis multiplex, demyelinating neuropathy. polyradiculopathy, sensory ganglionopathy. autonomic neuropathy	Immune-mediated mechanism rather than viral invasion of the nerves

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Cytomegalovirus (CMV)	Polyradiculopathy, mononeuropathy multiplex	Usually a painful neuropathy
Herpes simplex virus type 2	Lumbosacral radiculopathy	Genital herpetic lesions may not be present
Varicella-zoster virus	Radiculopathy	More commonly in thoracic dermatomes and trigeminal distribution
Epstein-Barr virus	Polyradiculopathy, sensory neuropathy	Mostly in patients who are munocompromised
West Nile virus	Motor neuronopathy	Acute myelitis due to viral invasion of anterior horn cells
Hepatitis C virus with cryoglobulinemia	Sensorimotor polyneuropathy, mononeuritis multiplex, radiculopathy	Immune-mediated mechanism associated with vessel injury
Treponema pallidum (syphilis)	Myelopathy, radiculopathy	Late state of neurosyphilis
Corynebacterium diphtheriae (diphtheria)	Demyelinating polyneuropathy	Prominent bulbar dysfunction with palatal weakness
Trypanosoma (or Schizotrypanum) cruzi (Chagas disease)	Autonomic neuropathy	Enteric neuron destruction leading to megaesophagus and megacolon

→ Thickened nerve

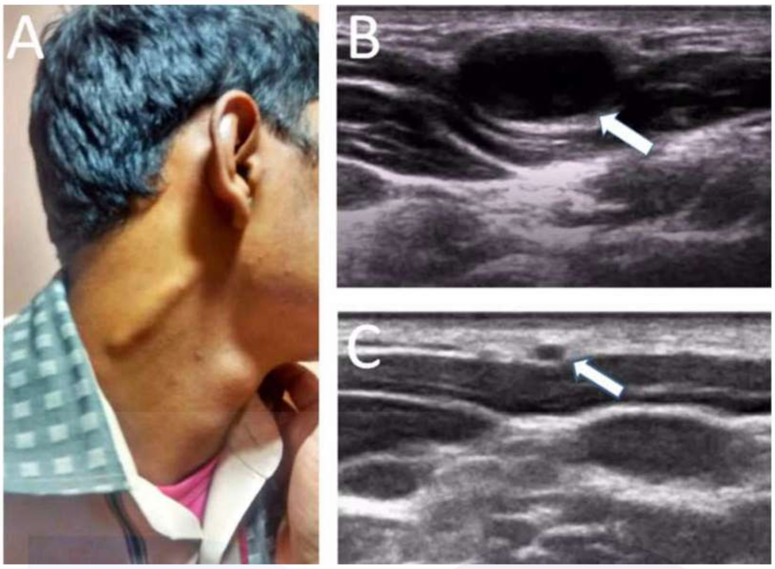

Fig: 7

HIV-Associated Peripheral Neuropathy
• Distal Symmetric Polyneuropathy (DSPN) • 30-50% patients • Mechanisms Direct - Systemic & CNS immune activation ART toxicity-Mitochondrial dysfunction • ART related: 3-6 months after initiation

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ART → stavucline, Didanosine, Zalcitabine → Neuropathy

- Vacuolar myelopathy seen in HIV

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Commonly Used Medications Associated With Polyneuropathy		
Agent	**Type**	**Notes**
Linezolid	Sensory neuropathy	May cause optic neuropathy and lactic acidosis
Chloramphenicol	Sensory-predominant axonal neuropathy	May cause optic neuritis
Dapsone	Motor-predominant axonal neuropathy	Cumulative dosage of >25 g is a risk factor
Metronidazole	Sensory-predominant axonal neuropathy, small fiber neuropathy	May cause optic neuropathy, cerebellar ataxia, encephalopathy
Nitrofurantoin	Sensorimotor axonal neuropathy, motor predominant neuropathy, sensory neuronopathy	Renal dysfunction is a risk factor
Isoniazid	Sensorimotor axonal neuropathy	Administration of pyridoxine prevents neuropathy development
Reverse transcriptase inhibitors (zalcitabine, didanosine, stavudine)	Sensory neuropathy, myopathy	Mitochondrial toxicity is the mechanism
Amiodarone	Mixed axonal and demyelinating sensorimotor neuropathy Sensorimotor polyneuropathy	Duration of therapy (>12 months) is a major risk factor
Disulfiram	Axonal sensorimotor neuropathy	May cause optic neuropathy
Phenytoin	Sensory neuropathy or neuronopathy	Duration of therapy (>5 years) is a major risk factor
Pyridoxine (vitamin B)	Myopathy more common than sensorimotor neuropathy	Fasting serum level needed to avoid spurious elevation
Colchicine	Type	Renal dysfunction is a risk factor
Isoniazid	Sensory neuropathy	Notes

Selected Chemotherapeutic Agents Associated With Polyneuropathy				
Class	Agent Name	Type	Electrophysiology	Notes
Vinca alkaloid	vinblastine, vinflunine (not available in the United States), vinorelbine	Sensorimotor; rarely pure motor, cranial, autonomic	Axonal, rarely demyelinating	Vincristine is the most neurotoxic coasting effect seen in 30% of patients
Taxane	Paclitaxel, docetaxel, cabazitaxel	Sensory more common than motor; sensory neuronopathy	Axonal	Mostly mild neuropathy, rarely dose-limiting
Platinum analogues	Cisplatin, carboplatin, oxaliplatin	Sensory neuronopathy, sensorimotor, peripheral nerve hyperexcitability	Axonal,	Coasting effect common; oxaliplatin may cause acute polyneuropathy
Proteasome inhibitors	Bortezomib	Sensory, sensorimotor, radiculaneuropathy	Axonal, rarely demyelinating	Nerve biopsy may show vasculitis
Thalidomide	Thalidomide	Sensory sensorimotor, autonomic	Axonal,	Constipation as the main finding of autonomic deficiency
Suramin	Suramin	Sensory, sensorimotor	Axonal, rarely demyelinating	Nerve biopsy may show inflammation

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- Critical illness polyneuropathy
- Prolonged IW stay
- Flaccid weakness
- Axonal neuropathy
- M>F
- Distal predominant weakness
- Critical illness myopathy
- ARDS/Asthma
- Received i.v high dose steroids
- CK
- EMG – denervation potential

Nerve biopsy 01:44:46

Indications for Nerve Biopsy
NERVE BIOPSY RESULTS SHOW DIAGNOSTIC ABNORMALITIES AND ARE ESSENTIAL FOR DIAGNOSIS
Vasculitis
Amyloidosis
Sarcoidosis
Hansen disease (leprosy)
Giant axonal neuropathy
Polyglucosan body disease
Tumor infiltration
NERVE BIOPSY RESULTS SHOW SUGGESTIVE ABNORMALITIES AND ARE ONLY SUPPORTIVE OF DIAGNOSIS
Charcot-Marie-Tooth disease types 1 and 3

Chronic inflammatory demyelinating polyradiculoneuropathy Paraproteinemic neuropathy (immunoglobulin M monoclonal gammopathy with anti-myelin-associated glycoprotein antibody)
*Consider combined distal nerve and muscle biopsies.

Amyloidosis → Congo red stain

Apple green birefringence

Immune mediate neuropathy 01:48:07

- Acute ↓ GBS
- Chronic ↓ CIDP

Guillain barre syndrome 01:50:03

Acute Inflammatory Demyelinating Polyradiculopathy

Etiopathogenesis

- Molecular mimicry
- Abnormal activation of T cells and b cells
- Infectious trigger +
- 10% of GBS have antecedent infection

↓

1.3 weeks before symptoms

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- Infections → G.I
  →Respiratory
- Common organism involved → C. jejune (m/c)
  CMV
  EBV
  Mycoplasma
  HIV
  Zika
- Clinical features
- Acute → subacute
- Motor & sensory manifestations
- Autonomic manifestations – rare
- Cranial nerve involvement

i. Motor manifestations
  - Starts in lower limbs
  - Ascending weakness
    ↓
    Proximal + Distal
  - Hypotonia
  - Areflexia

ii. Sensory manifestation – vague symptoms
  - Painful dysesthesias
  - Neck pain
  - Back pain
  - Vibration
  - Joint position sensations
  (Vibration and joint position sensations) affected

iii. Automatic

- Sever GBS → fluctuating BP
  Pulse rate variation
  Orthostatic hypotension
  } poor prognosis

iv. Cranial nerve involvement

- M/c – 7th nerve
- B/L LMN facial palsy → 50% patients of GBS
- Lower cranial nerve palsies → bulbar dysfunctions
- Rapid progressive weakness
- Prominent autonomic fluctuations
- Significant bulbar dysfunction

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Features Required for Guillain-Barré Syndrome Diagnosis	Features Supportive of Diagnosis	Features Casting Doubt on Diagnosis	Features That Rule Out Diagnosis
Progressive muscle weakness of more than one limb	Progression of weakness for 2–4 weeks	Marked persistent asymmetry of weakness	History of hexacarbon abuse
Areflexia or hyporeflexia	Symmetric involvement Mild sensory symptoms or signs Cranial nerve involvement Recovery begins 2–4 weeks after nadir Autonomic dysfunction Absence of fever Elevated CSF protein	Persistent bladder or bowel dysfunction Severe bladder or bowel dysfunction at onset >50 Leukocytes/mm³ in CSF Presence of polymorphonuclear leukocytes in CSF Sharp sensory level Central nervous system signs except in Miller Fisher syndrome–Bickerstaff brainstem encephalitis spectrum disorders	Acute intermittent porphyria Recent diphtheritic infection Poliomyelitis, botulism, toxic neuropathy, functional paralysis

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- > 4 weeks
  <8 weeks — subacute
- >8 weeks → CIDP
- Subtypes of GBS

Classification of Guillain-Barré Syndrome Subtypes and Variants
COMMON SUBTYPES
Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) Acute motor sensory axonal neuropathy (AMSAN)
Acute motor axonal neuropathy (AMAN)
RARE VARIANTS
Miller Fisher syndrome
Ataxic variant (Acute ataxic neuropathy)
Pharyngeal-cervical-brachial variant
Multiple cranial neuropathy variant
Facial diplegia with paresthesias
Paraparetic variant
Acute pandysautonomia

Most common – Acute Inflammatory Demyelinating Polyradiculopathy (AIDP)

- 90% of Miller fisher syndrome will have antibodies to anti GQ1 b
- MFS→ Ophthalmoplegia

Ataxia

Areflexia

- MFS – AIDP → weakness +

Subtypes of Guillain-Barré Syndrome (GBS)		
subtypes	FEATURES	ELECTRODIAGNOSIS
Acute inflammatory demyelinating polyneuropathy (AIDP)	Adults affected more than children; 90% of cases in Western world; recovery rapid; anti-GM1 antibodies (<50%)	Demyelinating
Acute motor axonal neuropathy (AMAN)	Children and young adults; prevalent in China and Mexico; may be seasonal; recovery rapid; anti-GD1a antibodies	Axonal
Acute motor sensory axonal neuropathy (AMSAN)	Mostly adults; uncommon; recovery slow, often incomplete; closely related to AMAN	Axonal
Miller Fisher syndrome (MFS)	Adults and children; ophthalmoplegia, ataxia, and areflexia; anti-GQ1b antibodies (90%)	Axonal or demyelinating

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Investigations

- Clinical assessment
- IOC: - electrodiagnosis study -NCS

  -Amplitude of potential - CMAP

  - latency

  - velocity
- 3 parameters are checked in nerve conduction study

  ↓

  - Motor
  - Sensory
  - F wave → to asses' proximal segments
- AIDP → increase distal latency

  Decrease conduction velocity

  Prolonged F wave latency

  Sometimes absent F wave

  Conduction blocks → 50% decrease in amplitude

  Temporal dispersion
- AMAN → axonal subtype

  Amplitude

  SNAPS
- AMSAN → axonal subtype

  Amplitude

  Motor & sensory affected

- Sural nerve spared in early part of illness
- CSF → n in 1st week

  -Albumin cytological dissociation

  ↓

  Increase CSF protein

  Nil / < 10 cells

  -HIV seroconversion → pleocytosis

- Increases predisposition of GBS in Hodgkin's Lymphoma
  SLE
  HIV
  Pleocytosis

Differentials

Differential Diagnostic Considerations in Guillain-Barré Syndrome
ACUTE POLYNEUROPATHIES
Hepatic porphyrias
Critical illness polyneuropathy
Diphtheria
Vasculitis
Toxins
Arsenic, thallium, organophosphates, lead
Neurotoxic fish and shellfish poisoning (ciguatoxin, tetrodotoxin, saxitoxin)
Buckthorn
POLYRADICULOPATHIES
Inflammatory or neoplastic meningoradiculopathies
Lyme radiculitis
Cytomegalovirus lumbosacral radiculomyelopathy
DISORDERS OF NEUROMUSCULAR JUNCTION
Botulism
Myasthenia gravis (crisis)

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Tick paralysis

MYOPATHIES

Hypokalemia

Hypophosphatemia Rhabdomyolysis

Polymyositis

Critical care myopathy

ANTERIOR HORN CELL DISORDERS

Poliomyelitis

West Nile and enterovirus poliomyelitis

CENTRAL NERVOUS SYSTEM DISORDERS

Transverse myelitis

Basilar artery thrombosis Rabies

- Diagnosis criteria
- Asbury cornblath (recent)

Clinical case definitions for diagnosis of GBS

Level 1 of diagnostic certainty

Bilateral AND flaccid weakness of the limbs

AND

Decreased or absent deep tendon reflexes in weak limbs

AND

Monophasic illness pattem and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau

AND

Electrophysiologic findings consistent with GBS

AND

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Cytoalbuminologic dissociation (i.e., elevation of CSF protein level above laboratory normal value AND CSF total white cell count <50 cells/μl)

AND

Absence of an identified alternative diagnosis for weakness

Level 2 of diagnostic certainty

Bilateral AND flaccid weakness of the limbs

AND

Decreased or absent deep tendon reflexes in weak limbs

AND

Monophasic illness pattern and interval between onset and nadir of weakness

between 12 h and 28 days and subsequent clinical plateau

AND

CSF total white cell count <50 cells/uL (with or without CSF protein elevation above laboratory normal value)

OR

If CSF not collected or results not available, electrophysiologic studies consistent with GBS

AND

Absence of identified alternative diagnosis for weakness

Level 3 of diagnostic certainty

Bilateral and flaccid weakness of the limbs

AND

Decreased or absent deep tendon reflexes in weak limbs

Monophasic illness pattern and interval between onset and nadir of weakness

AND

between 12 h and 28 days and subsequent clinical plateau

AND

Absence of identified alternative diagnosis for weakness

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- Variant → Bickerstaff encephalitis

  ↓

  -Anti GB1 b syndrome

  - Altered sensorium

  - Hyper -reflexia

Treatment

- Iv Ig (intravenous immunoglobin)

  ↓

  2g /kg → divided closes over 5 days

- Plasma exchange

  40-50 /kg single cycle x 5 cycles

  (Alternate days)

  7-14 days

  Increase costly

  Iv Ig = plasma exchange

  ↓

  Slight advantage in AMAN

  MFS

- No role for corticosteroids
- Monitor vital capacity & vitals
- DVT prophylaxis

Prognosis

- 95% → very good recovery
- Chronic immune mediated neuropathies

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Chronic Inflammatory Demyelinating Polyradiculopathy

- Gradual onset
- Protracted course (>8weeks)
- Autoimmune etiology
- T cells & B cells affected
- Antecedent infection not there
- Males >females
- 5-7th decades
- C/F
- 50% - typical CIDP

Typical CIDP

- Gradual
- Motor –symmetrical pro+ distal weakness

  UL 2 LL involvement
- Hypotonia
- Areflexia / hyperlexia
- Sensory→ numbness

  →vibration & joint position sense affected
- Autonomic → 25%
- Cranial nerve involvement – less common
- Tremors – neurogenic tremors
- Around 185 of cases may have acute onset

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Disorder	Acronym	Symptoms	Signs	Distinguishing Electrophysiology
Typical CIDP	CIDP	Proximal and distal weakness and numbness	Absent or reduced deep tendon reflexes in all limbs	Generalized demyelinating features
Atypical CIDP	DADS	Predominantly distal sensory more than motor	Deep tendon reflexes reduced or absent distally, may be normal or reduced in proximal areas	Distally accentuated demyelination
	MADSAM (Lewis-Sumner syndrome)	Asymmetric motor and sensory	Deep tendon reflexes may be normal in unaffected limb	Multifocal demyelination; motor and sensory
	Motor CIDP	Proximal and distal motor	Deep tendon reflexes generally reduced	Generalized motor demyelination; sensory spared
	Sensory CIDP; CISP	Proximal and distal sensory	Absent or reduced deep tendon reflexes in all limbs	Normal or small sensory responses; prolonged somatosensory evoked potentials; motor spared

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- DADS – distal acquired demyelinating symmetric neuropathy
- Most common – MADSAM
  ↓
- Multifocal acquired demyelinating sensory & symmetric → Neuropathy
- Also known as Lewis Sumner syndrome
- U/L> LL

- CISP- chronic inflammatory sensory polyradiculopathy

Secondary CIDP

Systemic Diseases Associated With Chronic Inflammatory Demyelinating Polyneuropathy
• Hematologic Diseases Monoclonal gammopathy Lymphoma Waldenström macroglobulinemia Castleman disease Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) • Diabetes Mellitus • Viral Infections HIV Hepatitis • Graft Versus Host Disease, • Organ Transplantation • Systemic Lupus Erythematosus • Inflammatory Bowel Disease • Malignancy • Nephrotic Syndrome • Investigation • NCS acquired demyelinating

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- Investigation
- NCS → acquired demyelinating

Typical CIDP:
- Prolonged distal latency
- Conduction velocity
- Conduction blocks
- Temporal dispersion
- Prolonged f wave latency (or) Absent f waves

- CSF - supportive

  Albumin cytologic disassociation

Diagnosis criteria

- EFNS -PNS criteria

Treatment

- 50-70 % show adequate treatment response
- Iv Ig – 2g/kg over 5 days

  Repeat every 3 weeks for 12 weeks

  ↓

  1g/kg

- Plasma exchange
- Corticosteroids
  - → Methyl prednisolone → 1g iv x s days ↓ oral steroids (1mg/kg)
  - → Dexamethasone
  - → Prednisone

- Steroids sparing agents

  ↓

  Azathioprine

  MMF

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- Antibodies cortactin – 1
  Neurofascin -155 } Better response to Rituximab
- 2018 – S.C immunoglobin
- Supportive treatment – DVT prophylaxis
  -physiotherapy

- Multifocal Motor neuropathy
  ↓
- Anti GM1 ganglioside antibodies
- UL- distal muscles
- Treatment – IV Ig
  No role for plasma exchange
  Corticosteroids
- NCS → Demyelination
  →Conduction blocks
- Monoclonal gammopathies
  ↓
- Multiple myeloma
- MGUS
- Vasculitis
- Paraneoplastic neuropathy.

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DISORDER OF PERIPHERAL NERVE

Lower Motor Neuro 00:00:30

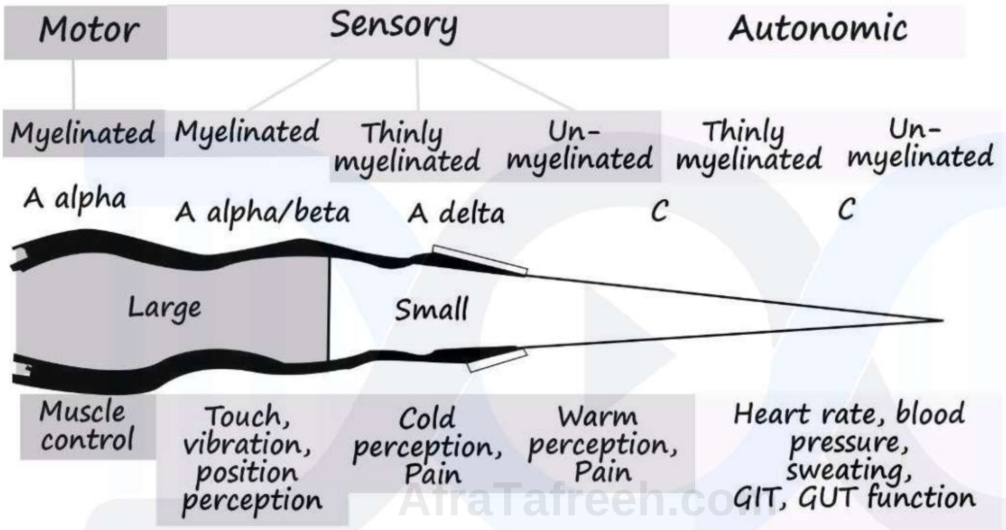
- Involves → Anterior horn cell.
- Roots
- Dorsal root ganglion
- Plexus
- Peripheral nerve
- NMJ
- Muscle
- Ganglion involved → Neuronopathy
- AHC involved → Motor neuronopathy
- DRG involved → Sensory neuronopathy (Ganglionopathy)

Classification 00:04:18

- Pathologic Classification of Neuropathic Disorders
- Neuronopathies (pure sensory or pure motor or autonomic):
- Sensory neuronopathies (ganglionopathies)
- Motor neuronopathies (motor neuron disease
- Autonomic neuropathies
- Peripheral neuropathies (usuay sensorimotor):
- Myelinopathies
- Axonopathies
- Large and small fiber

- Small fiber
- Aα, Aβ – Large myelinated fibers
- Aδ – small myelinated fibers
- C- Unmyelinated fibers

Causes of sensory neuropathy 0:06:44



- Peripheral nerve consists of motor, sensory and autonomous part →
  Hence called mixed nerve
- Motor is carried by large myelinated fibers (Aα)
- Sensory can be → Large myelinated
  →Small
  →unmyelinated
- Large myelinated fibred carry → vibration
  → Joint position sense
  → Two-point discrimination

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Classification of Peripheral Nerve Disease
Mononeuropathy
Plexopathy
Brachial plexopathy
Lumbar plexopathy
Sacral plexopathy
Radiculopathy
Cervical radiculopathy Thoracic radiculopathy Lumbosacral radiculopathy
Multiple mononeuropathy (mononeuropathy multiplex)
Polyneuropathy
Symmetrical polyneuropathy
Asymmetrical polyneuropathy
Polyradiculoneuropathy

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Etiology of Neuropathic Disorders
I. ACQUIRED
Dysmetabolic states
Diabetes mellitus
Neuropathy related to renal disease
Vitamin deficiency states (ex. Vitamin B12 deficiency)
Primary amyloidosis
Immune-mediated
Guillain-Barre Syndrome
Chronic inflammatory demyelinating polyneuropathy (CIDP)
Vasculitis
Infectious
Herpes zoster
Leprosy, Lyme, HIV, and Sarcoid related
Cancer related
Lymphoma, myeloma, carcinoma related
Paraneoplastic subacute sensory neuronopathy
Drugs or toxins
Chemotheraphy induced
Other drugs
Heavy metals and industrial toxin
Mechanical/Compressive
Radiculopathy
Mononeuropathy
Unknown etiology
Cryptogenic sensory and sensorimotor neuropathy

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Amyotrophic lateral sclerosis

II. HEREDITARY

Hereditary Motor Sensory Neuropathy (Charcot-Marie - Tooth disease)

Hereditary neuropathy with predisposition to pressure palsies

Familia! Brachial plexopathy

Familial amyloidosis

Porphyria

Other rare peripheral neuropathies

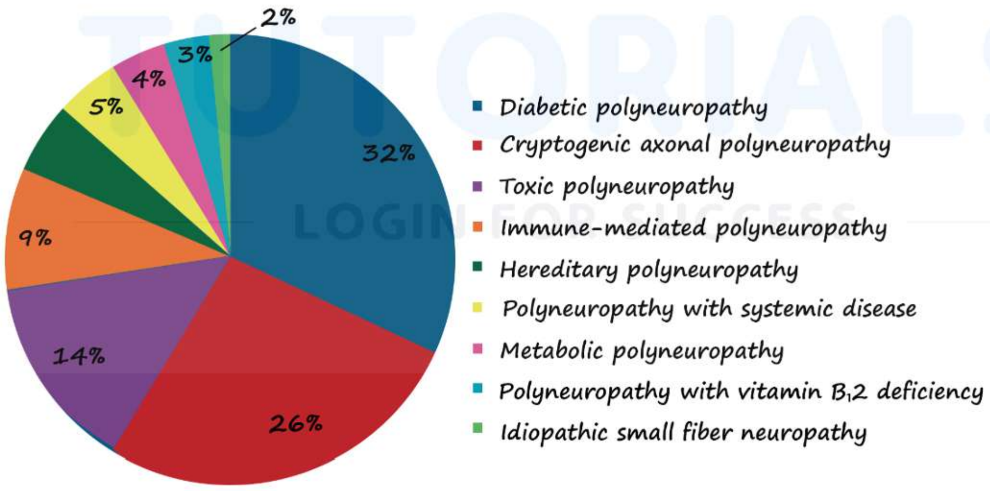
(Fabry's, metachromatic eukodystrophy,adrenolenkodystrophy, Refsum's disease etc.)

Motor neuron disease

Spinal muscular atrophy

Familial amyotrophic lateral sclerosis

X-linked bulbospinal muscular atrophy



Estimated prevalence of common polyneuropathy categories.

Neuropathy

Axonal | Demyelinating

Chronic axonal neuropathies
Drugs or toxins
-alcohol
- chemotherapeutic agents-for example, vincristine, cisplatinum
- organophosphate
- phenytoin
- antibiotics-for example, metronidazole, dapsone
- statins
Infections
- leprosy Borrelia
- HIV, HTLV1.
Connective tissue diseases
Sjogren's syndrome
systemic lupus erythematosus
rheumatoid arthritis
Metabolic
diabetes
Paraneoplastic
- lung, ovarian carcinoma
Inherited
- CMT 2 and X
- familial amyloid neuropathies
Vitamins -vitamin B12
- vitamin E
- pyridoxine toxicity
Endocrine
- hypothyroidism
Paraprotein
-lung, ovarian carcinoma
Inherited

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-CMT 2 and X

-familial amyloid neuropathies

Vitamins

-vitamin B1

-vitamin E

-pyridoxine toxicity

Endocrine

-hypothyroidism

Paraprotein

-myeloma

-Waldenstrom's disease

-benign monoclonal gammopathies

Demyelinating neuropathies

- Acute
  - Guillain Barre syndroje (GBS)
- Chronic
  - chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
  - paraproteinemia related amiodarone toxicity
  - Refsum's disease
  - Charcot-Marie-Tooth (CMT) types 1, X and AR CMT 1
  - metachromatic leucodystrophy
  - statins

Approach to peripheral neuropathy 00:24:45

Approach to Neuropathic Disorders: Seven Key Questions
1. What systems are involved? • Motor, sensory, autonomic, or combinations 2. What is the distribution of weakness? Only distal versus proximal and distal • Focal/asymmetric versus symmetric 3. What is the nature of the sensory Involvement? • Temperature loss or burning or stabbing pain (e.g., small fiber) • Vibratory or proprioceptive loss (e.g., large fiber) 4. Is there evidence of upper motor neuron Involvement? • Without sensory loss . With sensory loss 5. What is the temporal evolution? • Acute (days to 4 weeks) Subacute (4-8 weeks) • Chronic (>8 weeks) • Monophasic, progressive, or relapsing-remitting 6. Is there evidence for a hereditary neuropathy? • Family history of neuropathy . Lack of sensory symptoms despite sensory signs 7. Are there any associated medical conditions? Cancer, diabetes mellitus, connective tissue disease or other autoimmune diseases, infection (e.g., HIV, Lyme disease, leprosy) Medications including overs the counter doing that may cause a toxic

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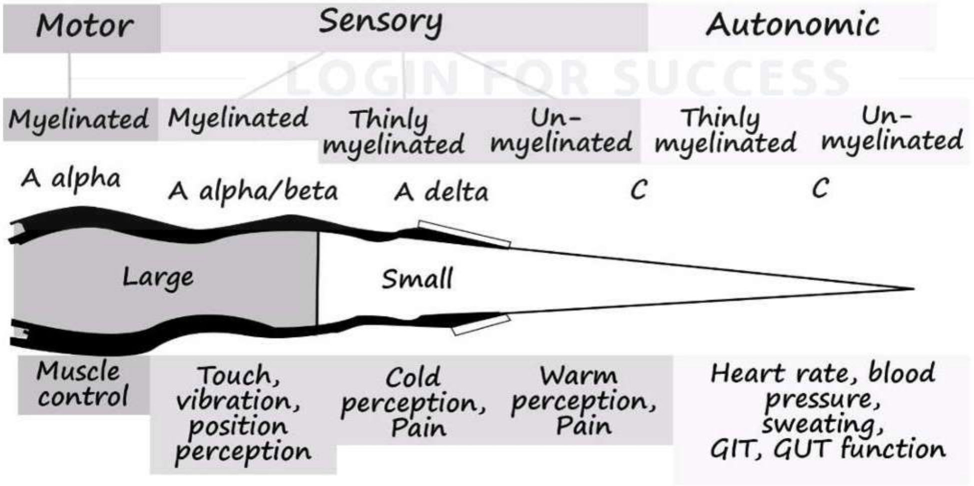
- Motor → weakness
- Sensory

Large fiber → Numbness, tingling, Pins& needles → Sensory ataxia

small fiber → burning

- Autonomic
  - orthostatic hypotension
  - palpitation
  - Bradycardia
  - constipation/Diarrhea
  - Erectile dysfunction
  - Bowel. Bladder dysfunction



Predominantly sensory neuropathies diabetes

- thiamine deficiency
- malignancy
- leprosy
- hereditary sensory neuropathies
- amyloid
- uraemia
- sarcoid

Neuropathies with Autonomic Nervous System Involvement
ACUTE Acute panautonomic neuropathy (autoimmune, paraneoplastic) Guillain-Barré syndrome Porphyria Toxic: vincristine, Vacor (rodenticide) **CHRONIC** Diabetes mellitus Amyloid neuropathy (familial and primary) Paraneoplastic sensory neuronopathy (malignant inflari matory sensory polyganglionopathy) Human immunodeficiency virus-related autonomic neuropathy Hereditary sensory and autonomic neuropath

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Neuropathic Disorders that Produce Asymmetric/Focal Weakness
Motor neuron disease
Amyotrophic lateral sclerosis
Radiculopathy-cervical or lumbosacral
Root compression from osteoarthritis
Root compression from herniated disc
Herpes zoster focal paresis (with rash)
Meningeal carcinomatosis and lymphomatosis
Sarcoid
Amyloid
Chronic immune sensory polyradiculopathy
Plexopathy-cervical, thoracic, or lumbosacral
Immune-mediated/Idiopathic
Neoplastic infiltration
Diabetic radiculoplexopathy (primarily lumbosacral)
Familial brachial plexopathy
Hereditary neuropathy with liability to pressure palsy
Mononeuropathy multiplex due to:
Vasculitis
Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM)
Multifocal motor neuropathy
Multifocal acquired motor axonopathy (MAMA)
Lyme disease
Sarcoid

Small-Fiber Neuropathies
Diabetes mellitus and impaired glucose tolerance
Amyloid neuropathy (early familial and primary)
HIV-associated distal sensory neuropathy
Hereditary sensory and autonomic neuropathies
Fabry disease
Tangier disease
Sjögren (sicca) syndrome
Cryptogenic small-fiber neuropathy

Large fiber Neuropathy → vit B12 deficiency
→ Friederichs ataxia
→ GB3
→ C1DP

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- Vit B12 deficiency

Hypocritic myelopathy
HIV
Vit E deficiency
] LMN+UMN involved

Some Causes of Polyradiculopathy
Structural
Spondyloarthropathy
Spinal stenosis
Radiation
Neoplastic
Non-Hodgkin lymphoma
Acute leukemia
Melanoma

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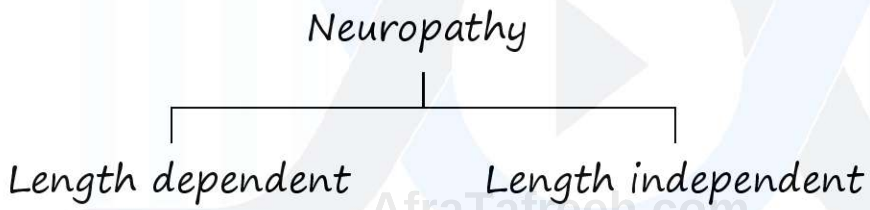
Carcinoma
Infectious
Lyme disease
Cytomegalovirus
Human immunodeficiency virus (HIV)
Tuberculosis
Herpes zoster
Schistosomiasis
Inflammatory
Sarcoidosis

Causes of Poly radiculomyelopathy
Hereditary
Porphyria
Inflammatory
Guillain-Barré syndrome
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome
Toxic
Arsenic
n-Hexane
Amiodarone
Diphtheria
Metabolic/Ischemic
Diabetic radiculoplexus neuropathy
Idiopathic
Idiopathic radiculoplexus neuropathy

Thenar atrophy in chronic bilateral carpal tunnel syndrome.

Fig: 1



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Axonal neuropathy

→ glove and stocking

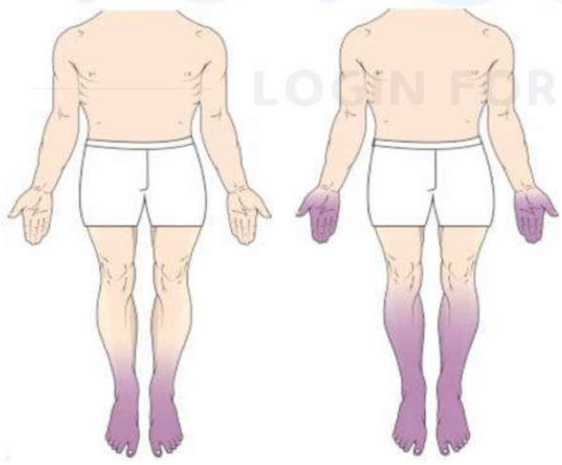

Fig: 2

→ length dependent polyneuropathy

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Common Causes of Length-dependent Polyneuropathy		
Category	Notable Examples	Estimated Prevalence of All Types
Diabetes mellitus	Large fiber sensory predominant small fiber Impaired glucose tolerance	33% 10-25% of above Unknown
Chronic idiopathic axonal polyneuropathy	Idiopathic	25 55%
Small fiber neuropathy	Idiopathic	2%
Hereditary	Charcot-Marie-Tooth disease (hereditary motor sensory neuropathy), hereditary sensory and autonomic neuropathy, hereditary motor neuropathy	5-33%
Metabolic	Vitamin B_1/other nutritional deficiency, end organ failure/critical illness polyneuropathy	12%
Toxic	Chemotherapy, industrial environmental toxins	14%
Inflammatory	Distal acquired demyelinating symmetric neuropathy associated with IgM monoclonal protein	9%

Neuropathies with Facial Nerve Involvement
Guillain-Barré syndrome
Lyme disease
Sarcoidosis
Chronic inflammatory demyelinating polyradiculoneuropathy (rare)
Human immunodeficiency virus 1 infection
Gelsolin familial amyloid neuropathy (Finnish)
Tangier disease

Polyneuropathies with Predominantly Upper-Limb Motor Involvement
Multifocal motor neuropathy
Lewis-Sumner variant of CIDP
Lead neuropathy*
Porphyria
Tangier disease
Familial amyloid neuropathy type 2
Hereditary motor neuropathy (uncommon forms)
*Frequently presents with wrist drop.

Neuropathies with Skin, Nail, or Hair Manifestations	
Disease	Skin, nail, or hair manifestations
Vasculitis	Purpura, livedo reticularis
Cryoglobulinemia	Purpura
Fabry disease	Angiokeratomas

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Leprosy	Skin hypopigmentation
Osteosclerotic myeloma (POEMS syndrome)	Skin hyperpigmentation
Variegate porphyria	Bullous lesions
Refsum disease	Ichthyosis
Arsenic or thallium intoxication	Mees lines
Thallium poisoning	Alopecia
Giant axonal neuropathy	Curled hair
POEMS, Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.	

Hereditary neuropathies 01:03:34

- m/c – chariot Marie tooth disease 9LMT)
- Young
- Positive family history
- Slowly progressive neuropathy

Chariot Maxie tooth disease 01:04:47

- Also referred Hereditary Motor Sensory neuropathy (HMNS)
- Subtypes
- CMT – I → most common (CMt-10)→ PMP 22 duplications

 2
 3
 4
 X

CLASSIFICATION OF CMT

- CMT1
  - AD - Predominantly demyelinating - Uniform conduction velocity slowing (<38 m/s)
- CMT2
  - AD- Predominantly axonal
  - Relatively normal velocities
  - Prom 12% htly reduced SNAP or CMAP
- CMT3
  - AD- severe demyelination - Infancy
- CMT4
  - AR- demyelinating
- CMTX
  - XL - Axonal

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Clinical Presentation

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CMT 1A CLINICAL PRESENTATION

- Age group: 1st - 3rd decade
- Distal predominant weakness
- Lower limb predominant weakness
- Sensory signs >>> Sensory symptoms

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Inverted champagne bottle

Appearance

Fig: 3

→ Onion bulb formation

↓

Due to demyelination 2 remyelination

↓

Thickened nerves

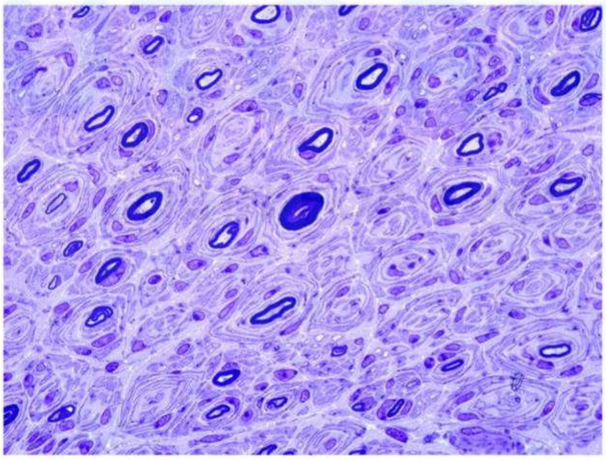

Fig: 4

HNPP 00:15:21

- Hereditary neuropathy with liability to pressure palsies
- Ad

- HASN– Hereditary sensory and autonomic neuropathy
- Hereditary Neuralgic amyotrophy

Rare Hereditary Neuropathies
Hereditary Disorders of Lipid Metabolism
Metachromatic leukodystrophy Krabbe's disease (globoid cell leukodystrophy Fabry's disease Adrenoleukodystrophy/adrenomyeloneuropathy Refsum's disease Tangier disease Cerebrotendinous xanthomatosis
Hereditary Ataxias with Neuropathy
Friedreich's ataxia Vitamin E deficiency Spinocerebellar ataxia Abetali poproteinemia (Bassen Korrzweig disease)
Disorders of Defective DNA Repair
Ataxia telangiectasia Cockayne's syndrome
Glant Axonal Neuropathy
Porphyria
Acute intermittent porphyria (AIP) Hereditary coproporphyria (HCP) Variegate porphyria (VP)
Familial Amylold Polyneuropathy (FAP)
Transthyretin related Gelsolin related Apolipoprotein A1 related

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Fabry's disease

- Due to α galactosidase A
- Painful acroparesthesia
- Cornea verticillate
- Vortex keratopathy
- Whorl like deposits
- Adrenoleukodystrophy / Adreno myeloneuropathy

↓

Peroxisomal ABC gene

Refsum's disease

- Phytanoyl CoA hydroxylase
- Cerebellar ataxia
- Retinitis pigmentosa
- CSF protein increased
- Short 4th metatarsal

Acquired neuropathy 01:23:11

- Diabetes mellites

Classification of Diabetic Neuropathies
GENERALIZED SYMMETRICAL POLYNEUROPATHIES
Distal sensory or sensorimotor polyneuropathy
Small-fiber neuropathy
Autonomic neuropathy

Large-fiber sensory neuropathy
FOCAL AND ASYMMETRICAL NEUROPATHIES
Cranial neuropathy. (Single or multiple)
Truncal neuropathy thoracic radiculopathy)
Limb mononeuropathy (single or multiple)
Lumbosacral radiculoplexopathy (amyotrophy, proximal neuropathy)
COMBINATIONS
Polyradiculoneuropathy Diabetic neuropathic cachexia

- Pain
- Asymmetry
- Wasting
- Wasting

(Asymmetry, Wasting, Wasting) — Bruns Garland syndrome

Amyloidosis

- Walden Strom's macroglobulinemia
- Multiple myeloma
- Lymphoma
- Small fiber neuropathy
- May cause automatic disinfection also

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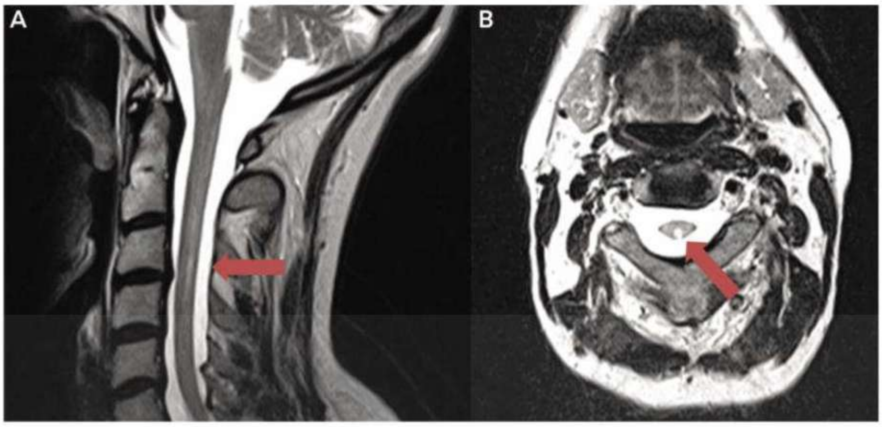
Vitamins and Minerals Commonly Implicated in Nutrient-deficiency Neuropathy			
Vitamin or Mineral	**Associated Condition**	**Nerve Fiber Type**	**Notes**
Cobalamin (vitamin B12)	Strict vegetarian diet, pernicious anemia, gastritis, inflammatory bowel disease, bariatric surgery, metformin, proton pump inhibitors	Large fiber sensory, myeloneuropathy	Corticospinal tract signs, cognitive impairment, macrocytic anemia
Folate	Inflammatory bowel disease, bariatric surgery, methotrexate, phenytoi	Large fiber sensory	May coexist with cobalamin deficiency, macrocytic anemia
Copper	Malnutrition, zinc toxicity, iatric surgery	Large fiber sensory, myeloneuropathy	Corticospinal tract signs, macrocytic anemia, neutropenia
Thiamine (vitamin B_1)	Alcoholism, malnutrition, bariatric surgery, malabsorption	Large fiber sensorimotor, polyradiculoneuropathy	Wernicke encephalopathy/ Korsakoff syndrome; serum measurement may not be reliable indicator
Pyridoxine (vitamin B6)	Isoniazid, alcoholism, bariatric surgery, malabsorption	Small fiber sensory more than large fiber sensory and motor involvement	Excess causes sensory ganglionopathy
α-Tocopherol (vitamin E)	Lipid malabsorption, bariatric surgery, genetic	Large fiber sensory	Notes

Tremor, cerebellar signs, myopathy



Inverted 'V' sign →SACD Fig: 5

Summary of infectious neuropathies		
Agent	**Type**	**Notes**
Mycobacterium leprae (leprosy)	Mononeuropathy multiplex, sensory neuropathy	Predilection for cool body regions such as extremities and face
Borrelia burgdorferi (Lyme disease)	Sensorimotor polyneuropathy, mononeuritis multiplex, radiculopathy	Neurologic manifestations can occur at acute and latent stages
Human immunodeficiency virus (HIV)	Axonal polyneuropathy. mononeuritis multiplex, demyelinating neuropathy. polyradiculopathy, sensory ganglionopathy. autonomic neuropathy	Immune-mediated mechanism rather than viral invasion of the nerves

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Cytomegalovirus (CMV)	Polyradiculopathy, mononeuropathy multiplex	Usually a painful neuropathy
Herpes simplex virus type 2	Lumbosacral radiculopathy	Genital herpetic lesions may not be present
Varicella-zoster virus	Radiculopathy	More commonly in thoracic dermatomes and trigeminal distribution
Epstein-Barr virus	Polyradiculopathy, sensory neuropathy	Mostly in patients who are munocompromised
West Nile virus	Motor neuronopathy	Acute myelitis due to viral invasion of anterior horn cells
Hepatitis C virus with cryoglobulinemia	Sensorimotor polyneuropathy, mononeuritis multiplex, radiculopathy	Immune-mediated mechanism associated with vessel injury
Treponema pallidum (syphilis)	Myelopathy, radiculopathy	Late state of neurosyphilis
Corynebacterium diphtheriae (diphtheria)	Demyelinating polyneuropathy	Prominent bulbar dysfunction with palatal weakness
Trypanosoma (or Schizotrypanum) cruzi (Chagas disease)	Autonomic neuropathy	Enteric neuron destruction leading to megaesophagus and megacolon

→ Thickened nerve

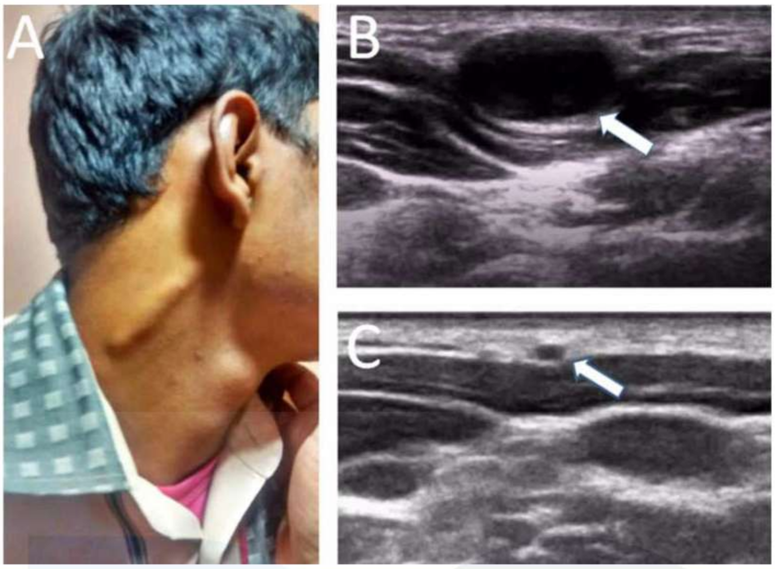

Fig: 7

HIV-Associated Peripheral Neuropathy
• Distal Symmetric Polyneuropathy (DSPN) • 30-50% patients • Mechanisms Direct - Systemic & CNS immune activation ART toxicity-Mitochondrial dysfunction • ART related: 3-6 months after initiation

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ART → stavucline, Didanosine, Zalcitabine } Neuropathy

- Vacuolar myelopathy seen in HIV

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Commonly Used Medications Associated With Polyneuropathy		
Agent	**Type**	**Notes**
Linezolid	Sensory neuropathy	May cause optic neuropathy and lactic acidosis
Chloramphenicol	Sensory-predominant axonal neuropathy	May cause optic neuritis
Dapsone	Motor-predominant axonal neuropathy	Cumulative dosage of >25 g is a risk factor
Metronidazole	Sensory-predominant axonal neuropathy, small fiber neuropathy	May cause optic neuropathy, cerebellar ataxia, encephalopathy
Nitrofurantoin	Sensorimotor axonal neuropathy, motor predominant neuropathy, sensory neuronopathy	Renal dysfunction is a risk factor
Isoniazid	Sensorimotor axonal neuropathy	Administration of pyridoxine prevents neuropathy development
Reverse transcriptase inhibitors (zalcitabine, didanosine, stavudine)	Sensory neuropathy, myopathy	Mitochondrial toxicity is the mechanism
Amiodarone	Mixed axonal and demyelinating sensorimotor neuropathy Sensorimotor polyneuropathy	Duration of therapy (>12 months) is a major risk factor
Disulfiram	Axonal sensorimotor neuropathy	May cause optic neuropathy
Phenytoin	Sensory neuropathy or neuronopathy	Duration of therapy (>5 years) is a major risk factor
Pyridoxine (vitamin B)	Myopathy more common than sensorimotor neuropathy	Fasting serum level needed to avoid spurious elevation
Colchicine	Type	Renal dysfunction is a risk factor
Isoniazid	Sensory neuropathy	Notes

Selected Chemotherapeutic Agents Associated With Polyneuropathy				
Class	Agent Name	Type	Electrophysiology	Notes
Vinca alkaloid	vinblastine, vinflunine (not available in the United States), vinorelbine	Sensorimotor; rarely pure motor, cranial, autonomic	Axonal, rarely demyelinating	Vincristine is the most neurotoxic coasting effect seen in 30% of patients
Taxane	Paclitaxel, docetaxel, cabazitaxel	Sensory more common than motor; sensory neuronopathy	Axonal	Mostly mild neuropathy, rarely dose-limiting
Platinum analogues	Cisplatin, carboplatin, oxaliplatin	Sensory neuronopathy, sensorimotor, peripheral nerve hyperexcitability	Axonal,	Coasting effect common; oxaliplatin may cause acute polyneuropathy
Proteasome inhibitors	Bortezomib	Sensory, sensorimotor, radiculaneuropathy	Axonal, rarely demyelinating	Nerve biopsy may show vasculitis
Thalidomide	Thalidomide	Sensory sensorimotor, autonomic	Axonal,	Constipation as the main finding of autonomic deficiency
Suramin	Suramin	Sensory, sensorimotor	Axonal, rarely demyelinating	Nerve biopsy may show inflammation

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- Critical illness polyneuropathy
- Prolonged IW stay
- Flaccid weakness
- Axonal neuropathy
- M>F
- Distal predominant weakness
- Critical illness myopathy
- ARDS/Asthma
- Received i.v high dose steroids
- CK
- EMG – denervation potential

Nerve biopsy 01:44:46

Indications for Nerve Biopsy
NERVE BIOPSY RESULTS SHOW DIAGNOSTIC ABNORMALITIES AND ARE ESSENTIAL FOR DIAGNOSIS
Vasculitis
Amyloidosis
Sarcoidosis
Hansen disease (leprosy)
Giant axonal neuropathy
Polyglucosan body disease
Tumor infiltration
NERVE BIOPSY RESULTS SHOW SUGGESTIVE ABNORMALITIES AND ARE ONLY SUPPORTIVE OF DIAGNOSIS
Charcot-Marie-Tooth disease types 1 and 3

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Chronic inflammatory demyelinating polyradiculoneuropathy Paraproteinemic neuropathy (immunoglobulin M monoclonal gammopathy with anti-myelin-associated glycoprotein antibody)
*Consider combined distal nerve and muscle biopsies.

Amyloidosis → Congo red stain

Apple green birefringence

Immune mediate neuropathy 01:48:07

Acute → GBS

Chronic → CIDP

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Guillain barre syndrome 01:50:03

Acute Inflammatory Demyelinating Polyradiculopathy

Etiopathogenesis

- Molecular mimicry
- Abnormal activation of T cells and b cells
- Infectious trigger +
- 10% of GBS have antecedent infection

↓

1.3 weeks before symptoms

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- Infections → G.I
  →Respiratory
- Common organism involved → C. jejune (m/c)
  CMV
  EBV
  Mycoplasma
  HIV
  Zika
- Clinical features
- Acute → subacute
- Motor & sensory manifestations
- Autonomic manifestations – rare
- Cranial nerve involvement

i. Motor manifestations
  - Starts in lower limbs
  - Ascending weakness
    ↓
    Proximal + Distal
  - Hypotonia
  - Areflexia

ii. Sensory manifestation – vague symptoms
  - Painful dysesthesias
  - Neck pain
  - Back pain
  - Vibration
  - Joint position sensations] affected

iii. Automatic

- Sever GBS → fluctuating BP, Pulse rate variation, Orthostatic hypotension } poor prognosis

iv. Cranial nerve involvement

- M/c – 7th nerve
- B/L LMN facial palsy → 50% patients of GBS
- Lower cranial nerve palsies → bulbar dysfunctions
- Rapid progressive weakness
- Prominent autonomic fluctuations
- Significant bulbar dysfunction

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Features Required for Guillain-Barré Syndrome Diagnosis	Features Supportive of Diagnosis	Features Casting Doubt on Diagnosis	Features That Rule Out Diagnosis
Progressive muscle weakness of more than one limb	Progression of weakness for 2-4 weeks	Marked persistent asymmetry of weakness	History of hexacarbon abuse
Areflexia or hyporeflexia	Symmetric involvement Mild sensory symptoms or signs Cranial nerve involvement Recovery begins 2-4 weeks after nadir Autonomic dysfunction Absence of fever Elevated CSF protein	Persistent bladder or bowel dysfunction Severe bladder or bowel dysfunction at onset >50 Leukocytes/mm³ in CSF Presence of polymorphonuclear leukocytes in CSF Sharp sensory level Central nervous system signs except in Miller Fisher syndrome-Bickerstaff brainstem encephalitis spectrum disorders	Acute intermittent porphyria Recent diphtheritic infection Poliomyelitis, botulism, toxic neuropathy, functional paralysis

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- > 4 weeks
  <8 weeks — subacute
- >8 weeks → CIDP
- Subtypes of GBS

Classification of Guillain-Barré Syndrome Subtypes and Variants
COMMON SUBTYPES
Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) Acute motor sensory axonal neuropathy (AMSAN)
Acute motor axonal neuropathy (AMAN)
RARE VARIANTS
Miller Fisher syndrome
Ataxic variant (Acute ataxic neuropathy)
Pharyngeal-cervical-brachial variant
Multiple cranial neuropathy variant
Facial diplegia with paresthesias
Paraparetic variant
Acute pandysautonomia

Most common – Acute Inflammatory Demyelinating Polyradiculopathy (AIDP)

- 90% of Miller fisher syndrome will have antibodies to anti GQ1 b
- MFS→ Ophthalmoplegia

Ataxia

Areflexia

- MFS – AIDP → weakness +

Subtypes of Guillain-Barré Syndrome (GBS)		
subtypes	FEATURES	ELECTRODIAGNOSIS
Acute inflammatory demyelinating polyneuropathy (AIDP)	Adults affected more than children; 90% of cases in Western world; recovery rapid; anti-GM1 antibodies (<50%)	Demyelinating
Acute motor axonal neuropathy (AMAN)	Children and young adults; prevalent in China and Mexico; may be seasonal; recovery rapid; anti-GD1a antibodies	Axonal
Acute motor sensory axonal neuropathy (AMSAN)	Mostly adults; uncommon; recovery slow, often incomplete; closely related to AMAN	Axonal
Miller Fisher syndrome (MFS)	Adults and children; ophthalmoplegia, ataxia, and areflexia; anti-GQ1b antibodies (90%)	Axonal or demyelinating

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Investigations

- Clinical assessment
- IOC: - electrodiagnosis study -NCS
  - -Amplitude of potential - CMAP
  - - latency
  - - velocity
- 3 parameters are checked in nerve conduction study

  ↓

  - Motor
  - Sensory
  - F wave → to asses' proximal segments
- AIDP → increase distal latency

  Decrease conduction velocity

  Prolonged F wave latency

  Sometimes absent F wave

  Conduction blocks → 50% decrease in amplitude

  Temporal dispersion
- AMAN → axonal subtype

  Amplitude

  SNAPS
- AMSAN → axonal subtype

  Amplitude

  Motor & sensory affected

- Sural nerve spared in early part of illness
- CSF → n in 1st week

  -Albumin cytological dissociation

  ↓

  Increase CSF protein

  Nil / < 10 cells

  -HIV seroconversion → pleocytosis

- Increases predisposition of GBS in Hodgkin's Lymphoma

  SLE

  HIV

  Pleocytosis

Differentials

Differential Diagnostic Considerations in Guillain-Barré Syndrome
ACUTE POLYNEUROPATHIES
Hepatic porphyrias
Critical illness polyneuropathy
Diphtheria
Vasculitis
Toxins
Arsenic, thallium, organophosphates, lead
Neurotoxic fish and shellfish poisoning (ciguatoxin, tetrodotoxin, saxitoxin)
Buckthorn
POLYRADICULOPATHIES
Inflammatory or neoplastic meningoradiculopathies
Lyme radiculitis
Cytomegalovirus lumbosacral radiculomyelopathy
DISORDERS OF NEUROMUSCULAR JUNCTION
Botulism
Myasthenia gravis (crisis)

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Tick paralysis

MYOPATHIES

Hypokalemia

Hypophosphatemia Rhabdomyolysis

Polymyositis

Critical care myopathy

ANTERIOR HORN CELL DISORDERS

Poliomyelitis

West Nile and enterovirus poliomyelitis

CENTRAL NERVOUS SYSTEM DISORDERS

Transverse myelitis

Basilar artery thrombosis Rabies

- Diagnosis criteria
- Asbury cornblath (recent)

Clinical case definitions for diagnosis of GBS

Level 1 of diagnostic certainty

Bilateral AND flaccid weakness of the limbs

AND

Decreased or absent deep tendon reflexes in weak limbs

AND

Monophasic illness pattem and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau

AND

Electrophysiologic findings consistent with GBS

AND

Cytoalbuminologic dissociation (i.e., elevation of CSF protein level above laboratory normal value AND CSF total white cell count <50 cells/μl)

AND

Absence of an identified alternative diagnosis for weakness

Level 2 of diagnostic certainty

Bilateral AND flaccid weakness of the limbs

AND

Decreased or absent deep tendon reflexes in weak limbs

AND

Monophasic illness pattern and interval between onset and nadir of weakness

between 12 h and 28 days and subsequent clinical plateau

AND

CSF total white cell count <50 cells/uL (with or without CSF protein elevation above laboratory normal value)

OR

If CSF not collected or results not available, electrophysiologic studies consistent with GBS

AND

Absence of identified alternative diagnosis for weakness

Level 3 of diagnostic certainty

Bilateral and flaccid weakness of the limbs

AND

Decreased or absent deep tendon reflexes in weak limbs

Monophasic illness pattern and interval between onset and nadir of weakness

AND

between 12 h and 28 days and subsequent clinical plateau

AND

Absence of identified alternative diagnosis for weakness

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- Variant → Bickerstaff encephalitis
  ↓
  - Anti GB1 b syndrome
  - Altered sensorium
  - Hyper -reflexia

Treatment

- Iv Ig (intravenous immunoglobin)
  ↓
  2g /kg → divided closes over 5 days
- Plasma exchange

  40-50 /kg single cycle x 5 cycles
  (Alternate days)
  7-14 days

  Increase costly

  Iv Ig = plasma exchange
  ↓
  Slight advantage in AMAN
  MFS
- No role for corticosteroids
- Monitor vital capacity & vitals
- DVT prophylaxis

Prognosis

- 95% → very good recovery
- Chronic immune mediated neuropathies

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Chronic Inflammatory Demyelinating Polyradiculopathy

- Gradual onset
- Protracted course (>8weeks)
- Autoimmune etiology
- T cells & B cells affected
- Antecedent infection not there
- Males >females
- 5-7th decades
- C/F
- 50% - typical CIDP

Typical CIDP

- Gradual
- Motor –symmetrical pro+ distal weakness

  UL 2 LL involvement
- Hypotonia
- Areflexia / hyperlexia
- Sensory→ numbness

  →vibration & joint position sense affected
- Autonomic → 25%
- Cranial nerve involvement – less common
- Tremors – neurogenic tremors
- Around 185 of cases may have acute onset

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Disorder	Acronym	Symptoms	Signs	Distinguishing Electrophysiology
Typical CIDP	CIDP	Proximal and distal weakness and numbness	Absent or reduced deep tendon reflexes in all limbs	Generalized demyelinating features
Atypical CIDP	DADS	Predominantly distal sensory more than motor	Deep tendon reflexes reduced or absent distally, may be normal or reduced in proximal areas	Distally accentuated demyelination
	MADSAM (Lewis-Sumner syndrome)	Asymmetric motor and sensory	Deep tendon reflexes may be normal in unaffected limb	Multifocal demyelination; motor and sensory
	Motor CIDP	Proximal and distal motor	Deep tendon reflexes generally reduced	Generalized motor demyelination; sensory spared
	Sensory CIDP; CISP	Proximal and distal sensory	Absent or reduced deep tendon reflexes in all limbs	Normal or small sensory responses; prolonged somatosensory evoked potentials; motor spared

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- DADS – distal acquired demyelinating symmetric neuropathy
- Most common – MADSAM
  ↓
- Multifocal acquired demyelinating sensory & symmetric → Neuropathy
- Also known as Lewis Sumner syndrome
- U/L> LL

- CISP- chronic inflammatory sensory polyradiculopathy

Secondary CIDP

Systemic Diseases Associated With Chronic Inflammatory Demyelinating Polyneuropathy
• Hematologic Diseases Monoclonal gammopathy Lymphoma Waldenström macroglobulinemia Castleman disease Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) • Diabetes Mellitus • Viral Infections HIV Hepatitis • Graft Versus Host Disease, • Organ Transplantation • Systemic Lupus Erythematosus • Inflammatory Bowel Disease • Malignancy • Nephrotic Syndrome • Investigation • NCS acquired demyelinating

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- Investigation
- NCS → acquired demyelinating

Typical CIDP
- Prolonged distal latency
- Conduction velocity
- Conduction blocks
- Temporal dispersion
- Prolonged f wave latency (or) Absent f waves

- CSF - supportive

  Albumin cytologic disassociation

Diagnosis criteria

- EFNS -PNS criteria

Treatment

- 50-70 % show adequate treatment response
- Iv Ig – 2g/kg over 5 days

  Repeat every 3 weeks for 12 weeks

  ↓

  1g/kg

- Plasma exchange
- Corticosteroids → Methyl prednisolone → 1g iv x 5 days ↓ oral steroids (1mg/kg)

  → Dexamethasone

  → Prednisone

- Steroids sparing agents

  ↓

  Azathioprine

  MMF

- Antibodies cortactin – 1
  Neurofascin -155 } Better response to Rituximab
- 2018 – S.C immunoglobin
- Supportive treatment – DVT prophylaxis
  -physiotherapy

- Multifocal Motor neuropathy
  ↓
- Anti GM1 ganglioside antibodies
- UL- distal muscles
- Treatment – IV Ig
  No role for plasma exchange
  Corticosteroids
- NCS → Demyelination
  →Conduction blocks
- Monoclonal gammopathies
  ↓
- Multiple myeloma
- MGUS
- Vasculitis
- Paraneoplastic neuropathy.

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DISORDER OF NEUROMUSCULAR JUNCTION

Myasthenia gravis 00:01:00

- NMJ disorder that effects post synapsis terminal
- Autoimmune disorder
- Bimodal age group

  Female: - 3rd and 4th decade

  Males: - 6th – 7th decade
- Females > Males (3:2).

Etiopathogenesis 00:03:57

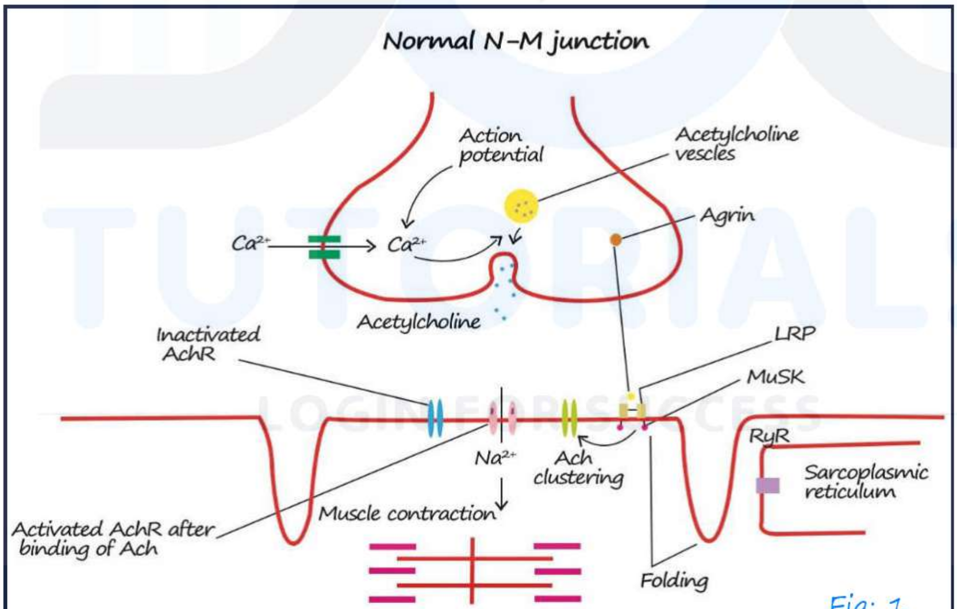

Fig: 1

- Lot of vesicles in motor nerve terminal contain Ach

- When a nerve action potential comes to presynaptic junction

↓

Initially there is calcium inflex into pre synaptic nerve terminal

↓

Causes vesicles to move towards neuromuscular junction

↓

Release of Ach

↓

Ach reaches synaptic cleft

↓

Binds with receptor (Ach R)

- Ach R is located in post synaptic part

↓

5 subunits → 2α

1β

1s

1γ or 1 epsilon

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- Binding of Ach-to-Ach R

↓

Activation of Ach R

↓

Influx of Na^+ from synaptic cleft to post synaptic Part though these channels

↓

Depolarization of post synaptic junction

↓

End plate potential (EPP) created

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- If EPP created is large enough, it results inaction potential
- This action potential turns into skeletal muscles contraction
- For proper functioning of Ach R and for proper arrangement of Ach R in post synaptic junction it is imperative that you have

  Certain substance like

  - Agrin
  - LPP (lipoproteins receptor protein)
  - MUSK 9 (muscle specific kinase)

  ↓

  Important for Ach R clustering

- In myasthenia gravis
  - Antibody production against Ach R (common)

    MUSK

    LR p4

    Agrin
  - NMJ transmission affected

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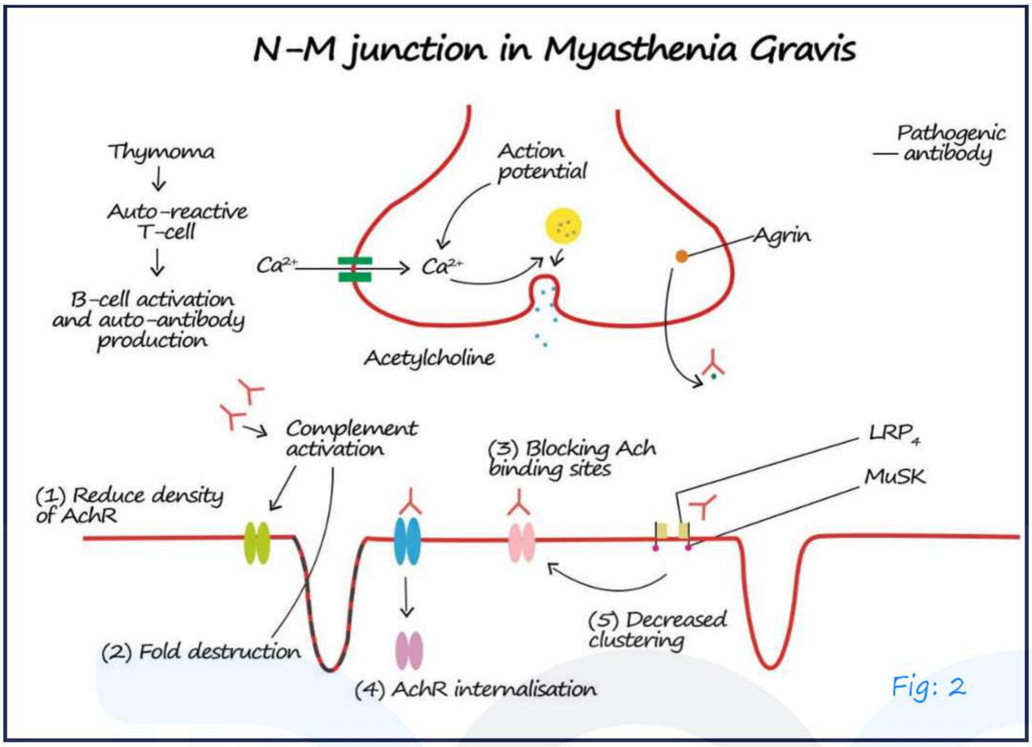

Fig: 2

i. Decreased number of Ach R in post synaptic part

ii. Post synaptic part flattened

iii. Clocking of Ach binding sites

iv. Internalization of Ach R

v. Decreased clustering

- Both B and T cells are important
- Thymus plays a important role in myasthenia Gravis
- Myoid or muscles like cells
- If EPP is created → decreased amplitude

Clinical features 00:15:33

- Ocular MG
- Generalized MG

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Core features

- Weakness 2 fatigability

  ↓

  Begins with lids 2 extra ocular muscles

  ↓

  - Ptosis
  - diplopia

- Ocular MG: - If a patient develops ptosis, diplopia & remains

  Like that for 3 years

  Proximal muscles weakness (predominantly symmetrical)

  ↓

  Limb girdle pattern of weakness

- Weakness worsens at end of the day
- Other features → dysarthria → Nasal Twang of voice

  →hoarseness of voice

  →Nasal regurgitation

  →Difficulty in swallowing

- Weakness may be aggravated due to underlying infection
- If myasthenia worsens→ there can be respiratory failure

  ↓

  Patient might require ventilator

  ↓

  Myasthenic crisis

- LMN type of weakness
- Hypotonia
- Deep tendon reflexes → normal
- No sensory manifestations

Fatigable ptosis – curtain sign Fig: 3

a. Left eyelid ptosis at rest and
b. Passive lifting of ptotic eyelid cause apparently normal eyelid to fall (enhanced ptosis) in a patient with MG

Vertical smile (snarling facies)

Screw closure of eyelids Fig: 4

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↓

Fatiguability

↓

Peek sign

Factors that Can Trigger or Worsen Myasthenia Gravis

- Surgery
- Pregnancy and postpartum period
- Hear
- Stress
- Viral infections
- Bone Marrow Transplantation
- Medications

Antibiotics

- Aminoglycosides
- Fluoroquinolones
- Tetracyclines
- Sulfonamides
- Penicillin's
- Nitrofurantoin
- Telithromycin
- Magnesium and magnesium containing medication (eg, Laxative, antacids)
- Botulinum toxin
- Interferon alfa
- D-Penicillamine
- Cardiovascular medications

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- Quinidine, quinine,
- Beta- blockers
- Calcium channer blockers

- Anesthetics (eg, methoxyflurane
- Neuromuscular blockers (eg, succinylcholine)
- Check point inhibitors (eg, pembrolizumab)

Associated condition 00:34:45

Associated disorders

- Disorders of thymus: thymoma, hyperplasia
- Other autoimmune neurological disorders: chronic inflammatory demyelinating polyneuropathy, neuromyelitis optica
- Other autoimmune disorders: Hashimoto's thyroiditis, Graves's disease, rheumatoid arthritis, systemic lupus erythematous, skin disorders, family history of autoimmune disorders
- Disorders or circumstance that may exacerbate myasthenia gravis: hyperthyroidism or hyperthyroidism, occult infection medical treatment for other conditions (see Table 440-4)

- 75% of myasthenia gravis have thymic involvement
  - 65% Thymic Hyperplasia
  - 10% thymoma

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Investigation 00:37:15

i. Most common – Icepack test

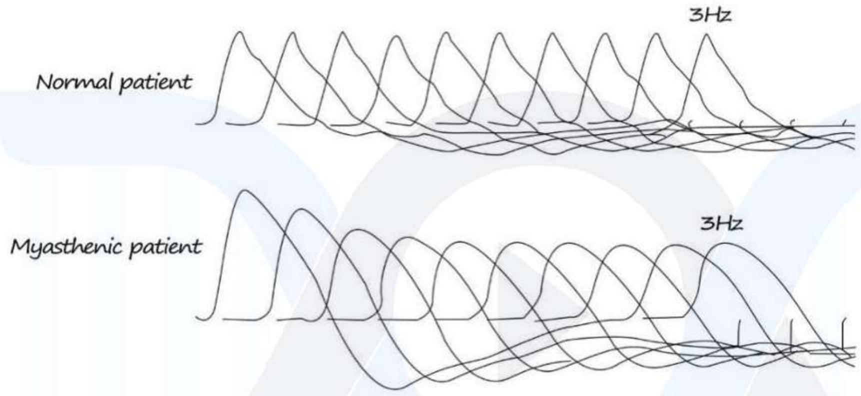
↓

Ptosis +

Close the eyes → Pack placed → improve for 2 mins

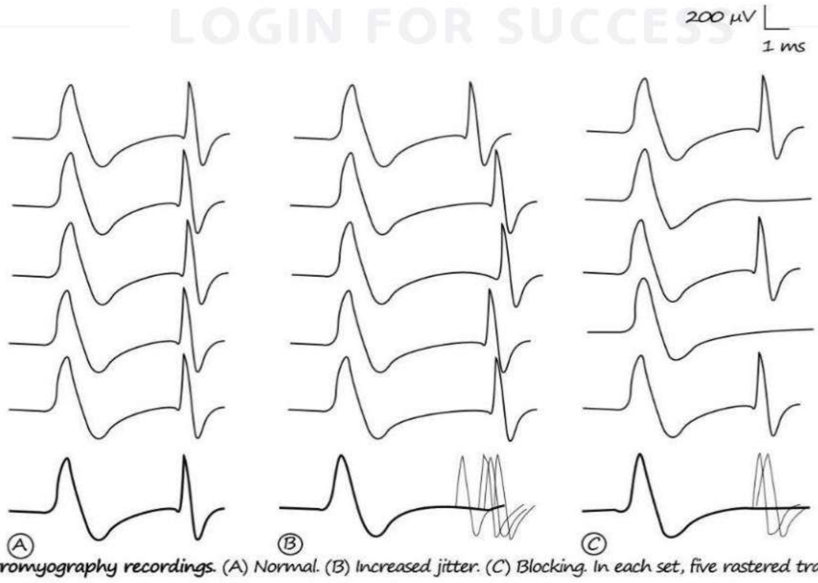
- cold will improve NMJ transmission

ii. Repetitive nerve stimulation (RNS)



- Low frequency RNS – 5 H2
- High frequency RNS – 50 H2

iii. Most sensitive → SF EMG (single fiber EMG)



Single-fiber electromyography recordings. (A) Normal. (B) Increased jitter. (C) Blocking. In each set, five rastered traces (top) and superimposed traces (bottom) are shown. Both increased jitter and blocking are seen in neuromuscular junction disorders.

- Single – fiber electromyography recordings

  a. Normal

  b. Increased jitter.

  c. Blocking.

  In each set, five rastered traced (top) and superimposed traces (bottom) are shown. Both increased jittler and blocking are seen in neuromuscular junction disorders.

  - Determine AP of each muscle fiber
  - Compare AP of individual 2 fiber
  - Last trace – superimposed trace of all the above
  - Jitteriness ⎤ – features of Mg
  - Blocking ⎦

iv. Edrophonium test (tensilon)

  - Edrophonium is basically Ach E inhibitor

    ↓

    Short acting

    ↓

    2 mg → Improvement of ptosis

  - Neostigmine is used now

v. Antibody estimation

  ↓

  - 85% with Generalized Mg → Ach R Ab
  - A50% with ocular MG → Ach R Ab
  - MUSK → females

    Prominent bulbar involvement

    Prominent facial involvement

    Very less responsive to Ache inhibitors

    Better response with plasma exchange & steroids

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Fig: 5

Predominant tongue atrophy in

MUSK + Myasthenia

↓

Triple furrowed tongue

- Antibodies against LRP4 Agrin

vi. Other investigations

- Ct thorax → look for thymic abnormality
- TFT
- ANA
- RA factor

Diagnostic Testing Based on Distribution of Weakness

Weakness	Besides test	Sens (%)	Edx test (Muscle)	Sens (%)	Immunologic test	Sens (%)
ocular	1. Edrophonium 2. Ice-pack	60-95 89	SFEMG (facial)	90	AChR-Ab	50
Oropharyngeal or generalized	None	-	1. RNS (limb/ (cranial) 2. SFEMG (limb/facial)	60 99	1. AchR-Ab 2. MuSK-Ab (If above neg)	85 40-50
*Only if ptosis is present.						

Diagnosis of Myasthenia Gravis (MG)

History

- Diplopia, ptosis, dysarthria, dysphagia, dyspnoea
- Weakness in characteristic distribution: proximal limbs, neck extensors. generalized
- Fluctuation and fatigue: worse with repeated activity, Improved by rest
- Effects of previous treatments

Physical examination

- Evaluation for ptosis at rest and following one minute of exercise, extraocular muscles and subjective diplopia, orbicularis oculi and oris strength, jaw opening and closure
- Assessment of muscle strength in neck an extremities
- Weakness following repeated shoulder abduction
- Vital capacity measurement
- Absence of other neurologic signs

Laboratory testing

- Anti-AChR radioimmunoassay: –85% positive in generalized MG; 50% in ocular MG; definite diagnosis if positive; negative result does not exclude MG; –40% of ACHR antibody-negative patients with generalized MG have anti- MuSK antibodies
- Repetitive nerve stimulation: decrement of >10% at 3 Hz: highly probable
- Single-fiber electromyography: blocking and jitter, with normal fiber density; confirmatory, but not specific
- Edrophonium chloride (Enlon") 2 mg + 8 mg IV: highly probable diagnosis if unequivocally positive For ocular or cranial MG: exclude intracranial lesions by CT or MRI

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Treatment 00:59:15

- Ocular MG
  - Pyridostigmine: - 30-60 mg Q4 H
  - Of bulbar involvement, pyridostigmine is given 30 mins before meals
- Ocular MG bot responding to pyridostigmine

&

Generalized Myasthenia gravies

↓

Corticosteroids

↓

1mg /kg

- Can be started in low dose and increased
  (10mg → 20mg → 30 →)
- In follow up – stop steroids and start steroids sporing agents

↓

-Azathioprine
-Mycophenolate
-Rituximab → useful in MUSK + MG

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Newer agents

- Eculizumab → Ach R Ab +ve Generalized Myasthenia gravis
- Efgartigimod -> Fc Rn inhibitor

Role of thymectomy

- Thymoma
- 18 - 65 year generalized Mg Ach R Ab +ve
- Refractory MG

Management of myasthenic crisis

- Ventilatory assistance
- Iv Ig → 2g /kg over 5 days
- Plasm's exchange → 40 - 50 ml/kg /exchange
- Peripheral steroids → ventilated patients
- Myasthenic crisis should be differentiated from cholinergic crisis

myasthenic	cholinergic crisis
pupils N	miotic pupils
Tensilon test ↓ Improvement	further worsens

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Differential diagnosis 01:11:54

- Chronic progressive external ophthalmoplegia (CPEO)
- Other disorders of NMJ

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CPEO 01:12:38

- Associated with - ptosis
  - Extra ocular involvement → No Diplopia
  - Proximal muscle weakness
- often occurs as a component of mitochondrial

Lambert Eaton myasthenic syndrome (LEMS) 00:13:57

- autoimmune pre-synaptic NMJ disorder
- auto antibodies against presynaptic voltage gated calcium
- channels (P/Q) calcium channel
- Clinical features: - proximal starts in LL and progresses in UL

  (Caudocranial progression)

  - Ocular involvement
  - Bulbar

  DTR diminished or absent

  Prominent autonomic symptoms

  ↓

  Dry mouth

  erectile dysfunction

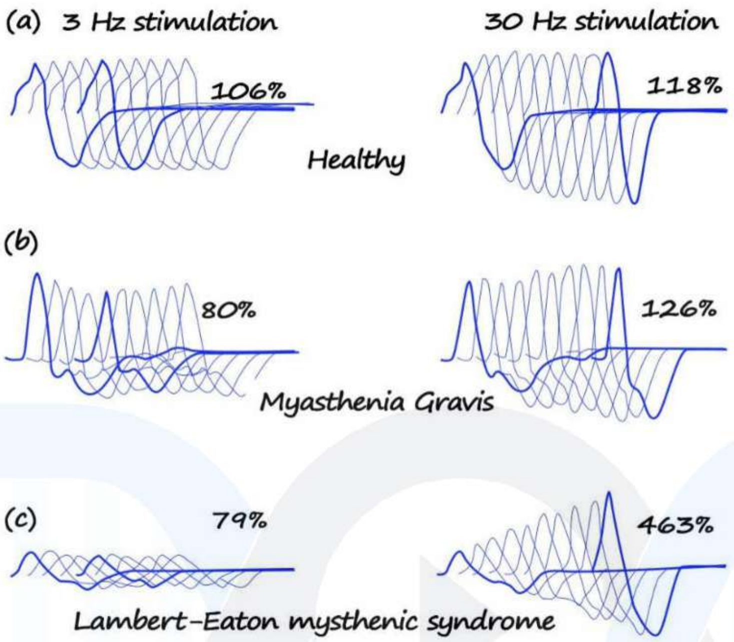
- In old people, may present as paraneoplastic syndrome

  ↓

  Most common cancer: - small cell lung cancer

Diagnosis

- RNS: - High frequency RNS



Treatment

- Doc: - 3,4 aminopyridine (acts via K^+ channels)
- Pyridostigmine

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Botulism 01:23:30

- Affects presynaptic NMJ
- Acute in onset
- Rapid progression
- Starts in bulbar region and descends
- Cranio- caudal progression
- Pupillary involvement +
- DTR → Early stages – N
- Late stages - dysfunctions
- Produces autonomic dysfunction

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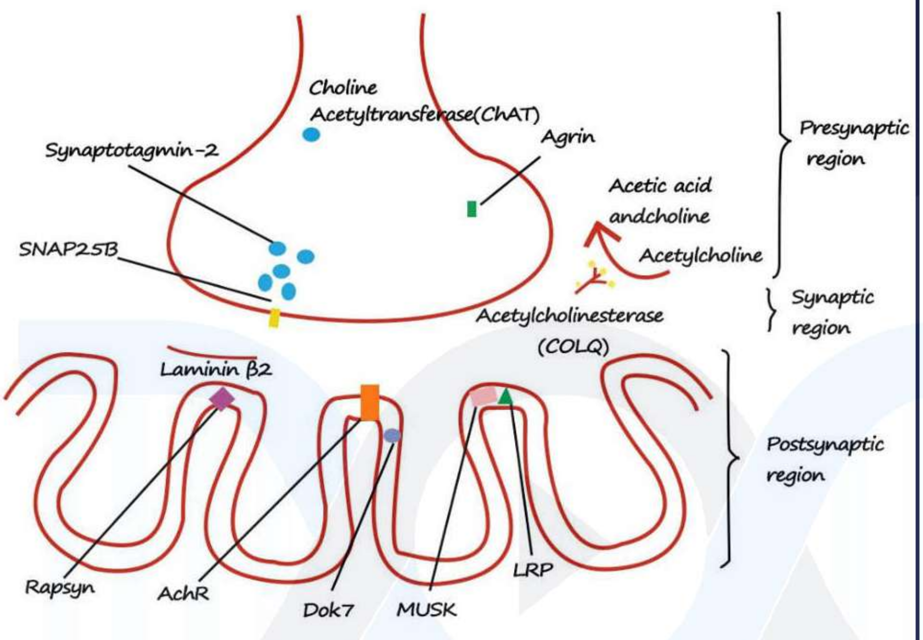
Congenital myasthenic syndrome 01:25:58

- Genetic defect in proteins → synaptotagamin

  →SNAP @% B



Neuromuscular endplate with locations of pre-synaptic, synaptic and postsynaptic pro teins involved in CMS Fig: 6

Neuromuscular endplate with locations of pre-synaptic, synaptic and posts synaptic proteins involved in CMS

- Most common subtype → defective in Ach R

  →Proximal muscle weakness

  →Ocular and bulbar involvement

  →Episodic apnea at birth

  ↓

  Cyanosis

  →Floppy infant

- Axis: _ Genetic study

  RNS – decremental response

- Treatment: - Ach E inhibitors
  - fluoxetine
  - Quinidine
  - Salbutamol

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MUSCLE DISORDERS

Muscle disorders

Negative symptoms | Positive

Myopathies

- Negative
  - Exercise intolerance
  - Fatigue
  - Muscle atrophy
  - Weakness
- Positive
  - Cramps
  - Contracture (electrically silent)
  - Muscle hypertrophy
  - Myalgia
  - Myoglobinuria
  - Stiffness

Muscle disorder	Anterior horn cell disorder
Weakness > wasting	Wasting > weakness

- Usual pattern of weakness in myopathies → symmetric

Proximal muscle weakness

↓

Limb girdle pattern

Classification of muscle disorders 00:05:42

Myopathies

- Congenital myopathies
  - Myofibrillar myopathy
- Muscular dystrophies
  - Dystrophinopathy (Becker muscular dystrophy)
  - Myotonic muscular dystrophy
  - Facioscapulohumeral muscular dystrophy
  - Limb-gridle muscular dystrophies
  - Oculopharyngeal muscular dystrophy
  - Dropped head/bent spine syndrome
- Metabolic myopathies
  - Glycogen storage defects
    i. Acid maltase deficiency
    ii. Debrancher deficiency
  - Disorder of lipid metabolism (rare)
  - Mitochondrial myopathies
  - Periodic paralysis

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Duchenne muscular dystrophy 00:07:09

- X-linked disorder
- Most common in males
- Mutated gene – Dystrophin gene
- DMD → complete absence of dystrophin gene
- BMD → partial absence of dystrophin gene

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Clinical features

- Birth history normal
- Age: 2-5years
- Symmetric proximal muscle weakness

↓

Proximal + Distal muscle weakness

- DTR – Normal early stages
- Calf muscle hypertrophy (pseudohypertrophy)
- Kyphosis

Grower's sign Fig: 1

- Lordosis

Fig: 2

- Cardiomyopathies
- Restrictive lung disease

Becker's dystrophy

- 5-15 years
- Survive upto 4th-5th decades
- Slow progressive disease

Fig: 3

Posterior axillary fold atrophy

↓

Valley's sign

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Investigations

- Genetic testing → Dystrophin
  - DNA from WBC's
  - Muscle biopsy
- CK increase
- MRI
  - Fatty infiltration
  - Pseudohypertrophy

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Treatment: - IQ decrease

- Deflazacort
- Eteplirsen → anti-sense oligonucleotide (ASO)
- Ataluren

Limb Girdle Muscular Dystrophy (LGMD) 00:18:41

Limb girdle muscular dystrophy

Type I → **AD**

Type II → **AR**

Classification of LGMDS

Disease	Gene	Affected protein
Commonly reported autosomal dominant (AD) LGMDs (type 1)		
LGMD 1A (myotilinopathy)	MYOT	Myotilin
LGMD 1B (laminopathy)	LMNA	Lamin
LGMD 1C (caveolinopathy)	CAV3	Caveolin
Commonly reported autosomal recessive (AR) LGMDS (type 2)		
LGMD 2A (calpainopathy)	CAPN3	Calpain
LGMD 2B (dysferlinopathy)	DYSF	Dysferlin
LGMD 2C, 2D, 2E and 2F (sarcoglycanopathy)	SGCG, SGCA, SGCB and SGCD, respectively	Gamma-sarcoglycan, alpha sarcoglycan, beta-sarcoglycan and delta-sarcoglycan
LGMD 2G (telethoninopathy)	TCAP	Telethonin

LGMD 2I (fukutin-related proteinopathy)	FKRP	Fukutin-related protein
LGMD 2 L (anoctaminopathy)	ANO5	Anoctamin 5
LGMD 2 M (fukutinopathy)	FKTN	Fukutin

Key clinical features of four common LGMDS	
Type of LGMD	Key clinical features
Calpainopathy	Onset in second decade, upper or lower limb girdle presentations, scapular winging, severe hip adductor weakness, toe walking, ankle contractures, abdominal herniae, marked serum CK elevation
Dysferlinopathy	Onset in second decade, early gastrocnemius weakness (Miyoshi), proximal limb girdle weakness (LGMD 2B), proximo distal form (most common), biceps lump and diamond on quadriceps, uncommonly, prominent tibialis anterior weakness, episodes of calf pains and swelling, marked serum CK elevation
Sarcoglycanopathies	Onset usually in first decade, DMD mimics, calf hypertrophy, proximal muscle weakness with Gowers' sign, ankle contractures, toe walking, scapular winging, marked serum CK elevation
Anoctaminopathy	Adult onset, males more severely affected, gastrocnemius weakness (Miyoshi like), persistent asymmetry of weakness, proximal weakness of lower girdle and quadriceps, very gradual progression, myalgias and exercise intolerance, marked serum CK elevation

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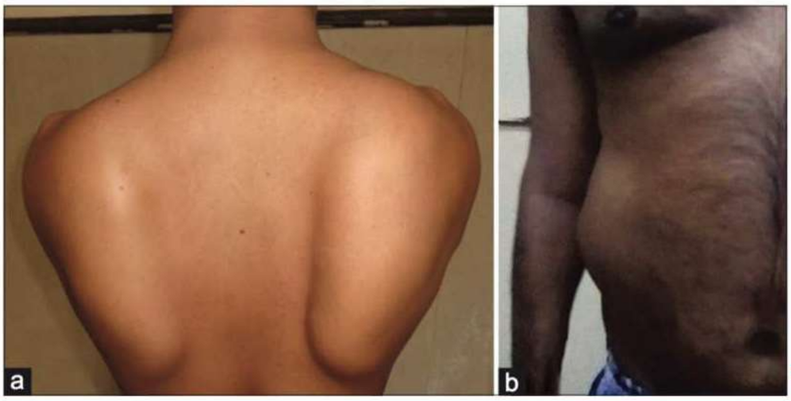
Fig: 4

a. Scapular winging
b. Abdominal hernia due to weakness of external oblique muscle

Fig: 5

a. Wasting of calf muscle
b. Diamond sign

Fig: 6

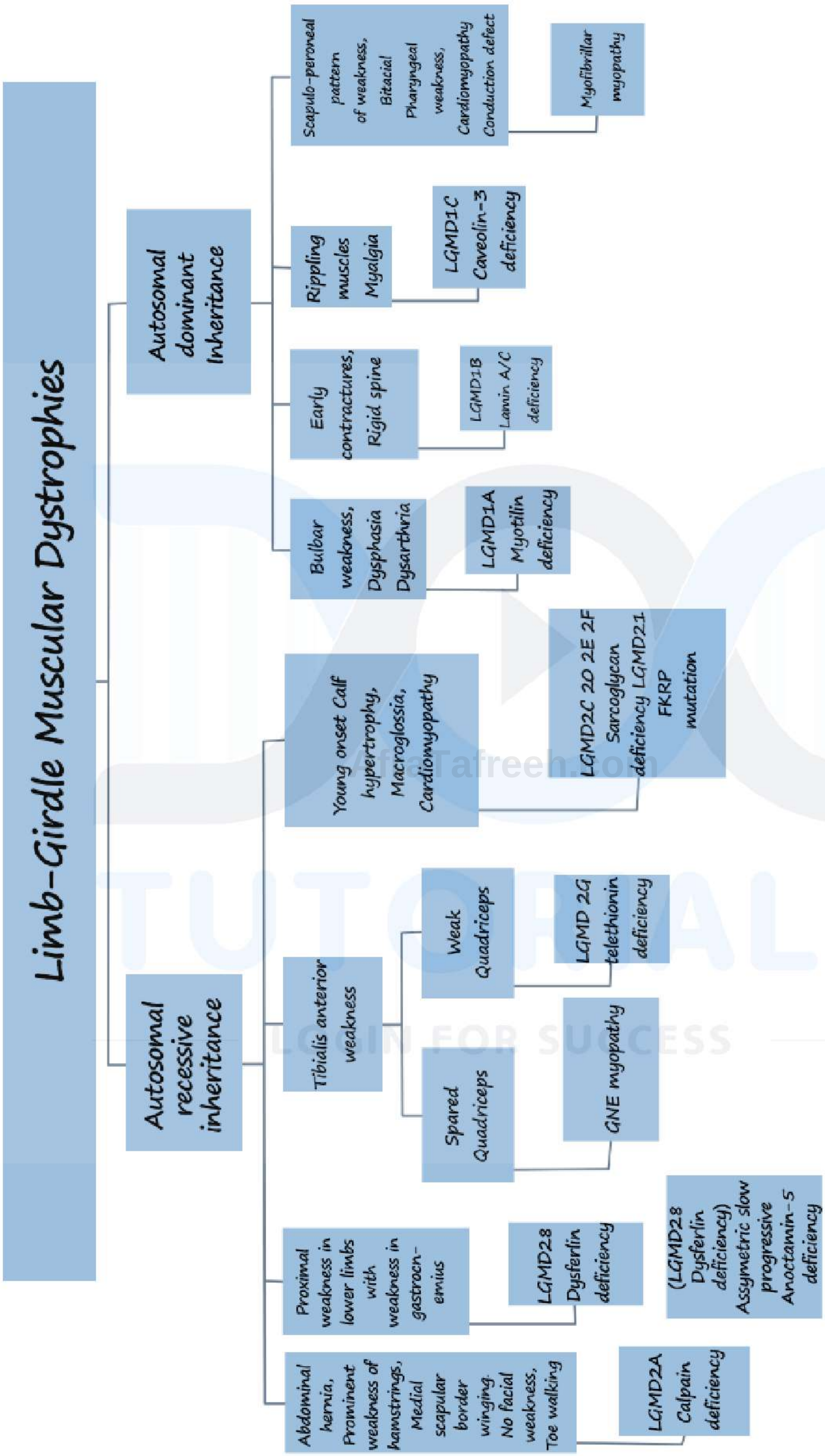
Limb-Girdle Muscular Dystrophies
Autosomal dominant Inheritance
Autosomal recessive inheritance
Bulbar weakness, Dysphasia Dysarthria
LGMD1A Myotilin deficiency
Early contractures, Rigid spine
LGMD1B Lamin A/C deficiency
Rippling muscles Myalgia
LGMD1C Caveolin-3 deficiency
Scapulo-peroneal pattern of weakness, Bifacial Pharyngeal weakness, Cardiomyopathy Conduction defect
Myofibrillar myopathy
Young onset Calf hypertrophy, Macroglossia, Cardiomyopathy
LGMD2C 2D 2E 2F Sarcoglycan deficiency LGMD21 FKRP mutation
Tibialis anterior weakness
Weak Quadriceps
LGMD 2G telethionin deficiency
Spared Quadriceps
GNE myopathy
Proximal weakness in lower limbs with weakness in gastrocnemius
LGMD28 Dysferlin deficiency
(LGMD28 Dysferlin deficiency) Assymetric slow progressive Anoctamin-5 deficiency
Abdominal hernia, Prominent weakness of hamstrings, Medial scapular border winging. No facial weakness, Toe walking
LGMD2A Calpain deficiency

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Fig: 7

a. Wasting of tibialis anterior muscle resulting in prominence of shin of tibia
b. Wasting of first dorsal interosseous muscle

Emery dreifuss muscular dystrophy 00:18:41

Gene mutations

Emerin → **XL**

Lamin A/C → **AD, AR**

- Early and prominent elbow contractures
- Humero-peroneal distribution
- Prominent cardiomyopathy

Fig: 8

Facio scapulohumeral dystrophy (FSHD) 00:32:31

- Autosomal dominant
- 2 types

2 types

FSHD type I → 95% deletion 4q (D_4Z_4 region)

FSHD type II → Deletion independent mechanism

Over activity of DOX_4 gene

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Clinical features

- Asymmetry
- Sleeps with eyes partially open

Fig: 9

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a. Bifacial weakness

b. Scapular winging, riding and poly-hill sign

c. Popeye sign

d. and e. Beevor's sign

- Coat's disease of eye → exudative retinal detachment due to retinal vasculopathy

  - Hearing loss

Myotonic dystrophy 00:40:05

- Associated with myotonia → Failure to relax
- Autosomal dominant
- Also known as DM

2 types

Type I	**Type II**
↓	↓
DM1	DM2
Steinert's disease	ZFNG gene
DMPK gene on chr.19	CCTG expansion
CTG repeat expansion	Proximal predominant weakness
Distal predominant weakness	

Muscle characteristics of myotonic dystrophy (DM), types I and II

Type of DM	Muscle groups commonly affected	Clinical myotonia (grip and percussion)
DM 1 (Steinert's disease)	Facial, neck, forearm, hand intrinsic, foot dorsiflexor	Common and often pronounced
DM II (Proximal myotonic myopathy)	Neck flexor, elbow extensor, finger flexor, hip flexor	Mild or in obvious

Muscle pain	Respiratory muscle involvement	Dysphagia and dysarthria
Yes (Rarely a presenting complaint)	Yes	Yes
Yes (Often a presenting complaint)	Uncommon	Uncommon

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- Predominant involvement of
  - Temporalis
  - Masseter
  - Facial

    ↓

  HATCHET FACIES

  Fish mouth appearance

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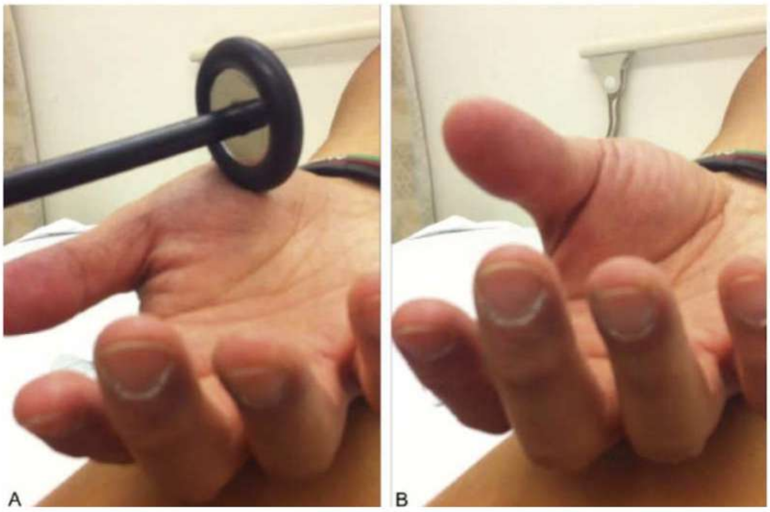
Fig: 10

- Multisystem disorder

Affected organs	Presenting features
Heart	PR prolongation, atrioventricular block, atrial tachycardia, risk of ventricular tachycardia and later-stage, left ventricular dysfunction. Patients are at risk of sudden cardiac death
Eyes	Premature cataracts (Christmas tree-like appearance)
Central nervous system	Behavioral and cognitive changes like apathy, executive dysfunction, memory disturbance and altered sleep habits. They may explain functional disabilities which are out of proportion to their muscle weakness
Endocrine system	Testicular atrophy, balding, erectile dysfunction and insulin resistance
Gastrointestinal tract and liver	Constipation, gall bladder stones, elevated liver enzymes and dyslipidemia
Cancer	For unknown reasons, DM 1 patients are at risk of cancer of thyroid gland, ovary, choroidal melanoma

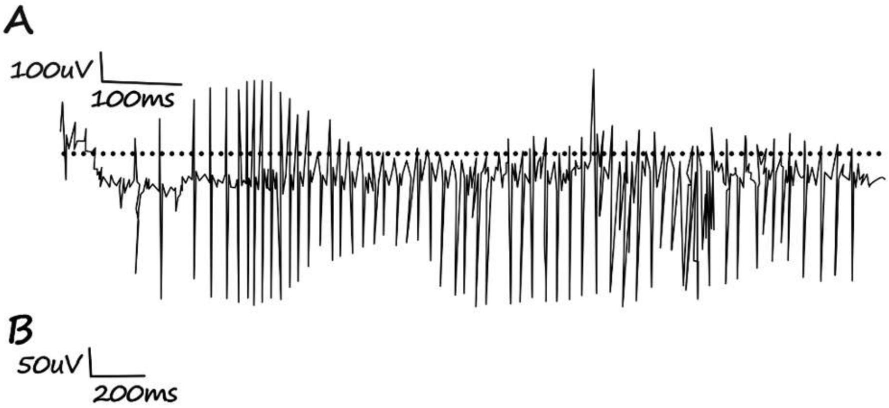


Percussion myotonia Fig: 11

Tongue myotonia Fig: 12

Diagnosis

- Genetic testing – Repeat expansion
- EMG – myotonic discharge



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Treatment

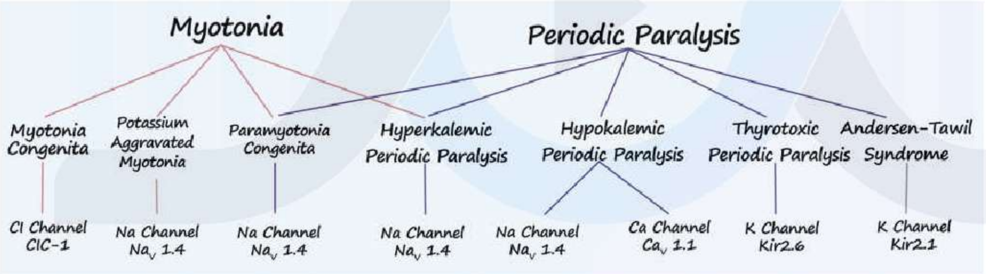
- Mexiletine
- Phenytoin

Muscle channelopathies 00:51:59

- Problem in Ion channel
- Alteration in muscle membrane excitability

Emerin → **XL**

Lamin A/C → **AD, AR**



	Myotonia Congenita	Paramyotonia Congenita	Other Sodium Channel Myotonia	Hyperkalemic periodic paralysis
Gene	CLCN1	SCN4A	SCN4A	SCN4A
Chromosome	7935	17Q23	17Q23	17Q23
Clinical features	Myotonia	Myotonia episodic weakness	Myotonia	Episodic weakness myotonia
Triggers	Cold (some patients)	Cold	Potassium (Some patients)	Potassium rest after exercise
Acute treatment	n/a	n/a	n/a	Carbohydrate/ glucose
Chronic treatment	Mexiletine, phenytoin, procainamide	Mexiletine, phenytoin, procainamide	Mexiletine, phenytoin, procainamide	Acetazolamide, dichlorphenamide

			, acetazolamide	
Exercise testing	Short exercise test (SET): Postexercise decrement, rapid return to baseline	SET: Postexercise decrement, facilitated by repetition or cold	SET: Often nondiagnostic	Long exercise test (LET): Postexercise decrement
Laboratory features	n/a	n/a	n/a	Ictal high potassium
Commercially available genetic testing	Yes	Yes	Yes	Yes

- Myotonic congenita

AD → Thomsen's disease

AR → Becker's disease

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- Isometric contraction of abductor digiti minimi
- Short exercise test and long exercise test

Short exercise test → Myotonia group

Long exercise test → Episodic weakness group

- Para myotonia congenita worsens with exercise

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Hypokalemic Periodic Paralysis	Andersen-Tawil Syndrome	Thyrotoxic Periodic Paralysis
CACNA1S, SCN4A	KCNJ2	KCNJ18
1932, 17q23	17q24	17b
Episodic weakness	Episodic weakness, premature ventricular contractions, ventricular tachyarrhythmia	Episodic weakness
Carbohydrates, rest after exercise	Rest after exercise, carbohydrates (some patients), potassium (some patients)	Thyrotoxicosis
Potassium oral, rarely IV	Potassium (if attacks associated with hypokalemia)	Potassium, adrenergic blocking agents
Potassium, acetazolamide, dichlorphenamide, potassium-sparing diuretic	Potassium, (if attacks associated with hypokalemia), acetazolamide, dichlorphenamide, potassium-sparing diuretic	Treatment of thyrotoxicosis
LET: Postexercise decrement	LET: Postexercise decrement	LET: postexercise decrement (when symptomatic)
Ictal low potassium	Ictal high/low potassium	Ictal low potassium, elevated thyroid hormone
Yes	Yes	No

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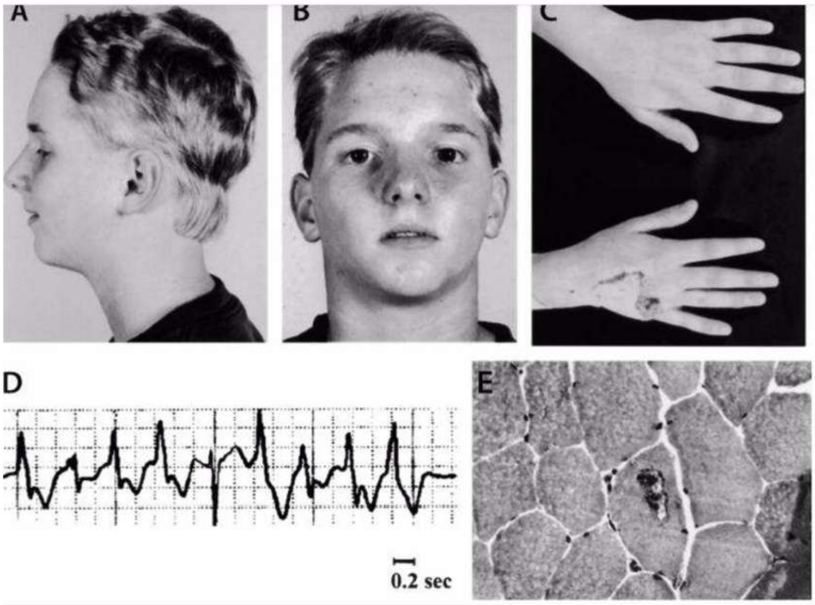

Fig: 13

Metabolic myopathies 01:11:10

- Can present with → Rhabdomyolysis, Myoglobinuria
  → Progressive muscle weakness

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Metabolic Myopathies in Skeletal Muscle

- Glycogen-Storage Disease (GSD)
  - McArdle disease/GSD5 (myophosphorylase deficiency)
  - Tarui disease/GSD7 (phosphofructokinase deficiency)
  - GSD9 (phosphorylase b kinase deficiency)
  - GSD10 (phosphoglycerate mutase deficiency)
  - GSD11 (lactate dehydrogenase deficiency)
  - GSD12 (aldolase A deficiency)
  - GSD13 (β-enolase deficiency)
  - Phosphoglucomutase deficiency

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- Phosphoglycerate kinase 1 deficiency
- Fatty Acid Oxidation Defect
  - Carnitine palmitoyltransferase II deficiency
  - Trifunctional protein deficiency
  - Very-long-chain acyl-coenzyme A dehydrogenase deficiency
- Mitochondrial Myopathy
  - Mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS)
  - Myoclonic epilepsy with ragged red fibers (MERRF)
  - Chronic progressive external ophthalmoplegia
  - Kearns-Sayre syndrome
  - Complex IV deficiency

Most common ardle's

- Due to deficiency of myophosphorylase
- Glycogen storage disease type V
- Second wind phenomenon

Pompe disease

- Due to deficiency of alpha glucosidase/Acid maltase
- Clinical presentation – 3 forms
- Infantile – Fatal, Life span <1.5years
- Childhood – DMD → Delayed motor milestones
- Adult – 3rd & 4th decade
- Macroglossia
- Cardiomyopathy

- Ck increases
- Enzyme replacement therapy available
- Phosphofructokinase deficiency and phosphoglycerate kinase 1 deficiency cause hemolytic anemia

Mitochondrial myopathies

- Maternal inheritance
- Mitochondrial gene → Maternal DNA
  → Nuclear DNA
  ↓
  Mendelian inheritance
- Clinical features – Chronic progressive external ophthalmoplegia skeletal muscle + CNS involvement pure myopathy

CPEO → Affects nuclear DNA

- Ptosis
- Progressive ophthalmoplegia
- No Diplopia
- Proximal muscle weakness

Kearns sayre syndrome

- Mitochondrial DNA deletion
- Classical triad → Age < 20years
  → CPEO
  → Retinitis pigmentosa

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- Cerebellar ataxia
- CSF protein > 100mg/dl
- Cardiac conduction abnormalities

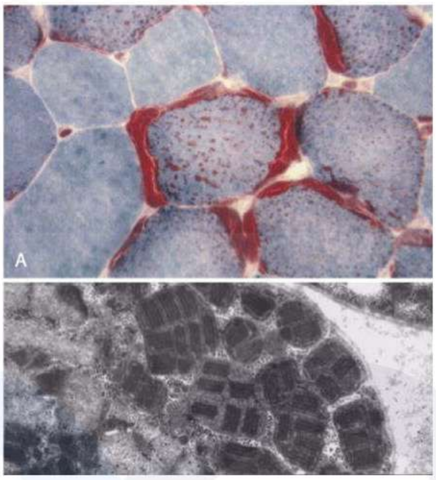

Fig: 14

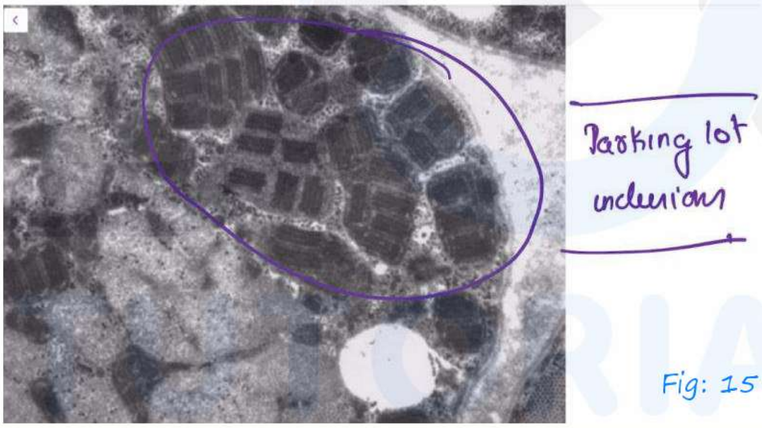

Fig: 15

Clinical Features Suggesting Specific Metabolic Myopathies

History	Disorder (Descending Likelihood)
Rhabdomyolysis/ pigmenturia	Glycogen – storage disease (GSD), fatty acid oxidation defects, mitochondrial myopathies
Myalgia > cramps with endurance sports	Mitochondrial myopathies
Myalgia/cramps with power/sprint sports	Glycogen – storage disease

Symptoms triggered by fasting or superimposed illness	Fatty acid oxidation defects, mitochondrial myopathies
Gout	Glycogen storage disease
Nausea/vomiting with exercise	Mitochondrial myopathies, GSD7
Multiple system involvement	Mitochondrial myopathies
Family history	
X – linked	Phosphorylase b kinase deficiency, phosphoglycerate kinase 1 deficiency
Maternal	Mitochondrial myopathies (mitochondrial DNA only)
Autosomal recessive/consanguineous	Carnitine palmitoyl transferase II deficiency, most glycogen storage diseases, nuclear encoded mitochondrial myopathies

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Treatment of mitochondrial myopathies

- Mitochondrial cocktail: Coenzyme Q10
  Vitamin E
  Alpha – Lipoic acid
  Creatine monohydrate
- L – Arginine
- L – carnitine

Endocrine myopathies 01:30:42

- Thyroid dysfunction
  - Hypothyroidism
  - Hyperthyroidism

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- Thyroid opthalmopathy
- Channelopathy (periodic paralysis)

- Parathyroid disturbance
- Adrenal disturbance
  - Cushing syndrome
  - Adrenal insufficiency
- Gonadal dysfunction
  - Testosterone deficiency
- Carcinoid syndrome
- Diabetic (myonecrosis)
- Acromegaly

Hypothyroidism

- Cramps → Symmetric proximal muscle weakness
- In adults → Hoffmann syndrome
- In children → Kocher debre semalaigne syndrome
- Muscle tissue is replaced by glycosaminoglycan's and fatty tissue

  ↓

  Pseudohypertrophy

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Drug induced myopathies 01:38:34

Drugs	Major Toxic Reaction
Lipid Lowering agents - HMG-CoA reductase - Inhibitors - Fibric acid derivatives - Nilacin (nicotine acid)	Drugs belonging to all three of the major classes of lipid-lowering agents can produce a spectrum of toxicity; asymptomatic serum creatine kinase elevation, myalgias, exercise-induced pain, rhabdomyolysis, and myoglobinuria.
Glucocorticoids	Acute, high – dose glycocorticoid treatment can cause acute quadriplegic myopathy. These high doses of steroids are often combined with non-depolarizing neuromuscular blocking agents but he weakness can occur without their use. Chronic steroid administration produces predominantly proximal weakness.
Non depolarizing neuromuscular blocking agents	Acute quadriplegic myopathy can occur with or without concomitant glucocorticoids.
Zidovudine	Mitochondrial myopathy with ragged red fibers
Drugs of abuse - Alcohol - Amphetamines - Cocaine - Heroin phencyclidine - Meperidine	All drugs in this group can lead to wide spread muscle breakdoen, rhabdomyolysis, and myoglobinuria. Local injections cause muscle necrosis, skin induration, and limb contractures.
Autoimmune myopathy - Statins - Check point inhibitors - O- pencillamine	Use of statins may cause an immune mediated necrotizing antibody. Check point inhibitors can be complicated by myositis, myasthenia gravis, and immune mediated neuropathies, myasthenia gravis has also been reported with penicillamine.
Amphophilic cationic drugs - Amiodarone - Chloroquine - Hydroxychloroquine	All amphophilic drugs have the potential to produce painless, proximal weakness associated with necrosis and autophagic vacuoles in the muscle biopsy.
Antimicrotubular drugs - Calchicine	This drug produces painless, proximal weakness especially in the setting of renal failure. Muscle biopsy shows necrosis and fibers with autophagic vacuoles.

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- IMNM → Immune mediated necrotizing myopathy

↓

Develop anti HMGCOA reductase antibody

↓

Severe muscle necrosis

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DISEASES OF SPINAL CORD

Anatomy of Spinal Cord 00:01:56

Basic anatomy – spinal cord
• Length: 42-45 cm • Extension: Medulla to conus medullaris • 31 spinal segments with cervical and lumbar enlargements • Duramater: up to S2 • Arachnoid: Up to S2 • Piamater: beyond C. medullaris, continues as filum terminal up to coccyx • Cauda equina lies in a pool of CSF – Lumbar cistern

- Area of spinal cord which gives rise to one spinal nerve is called spinal segment.

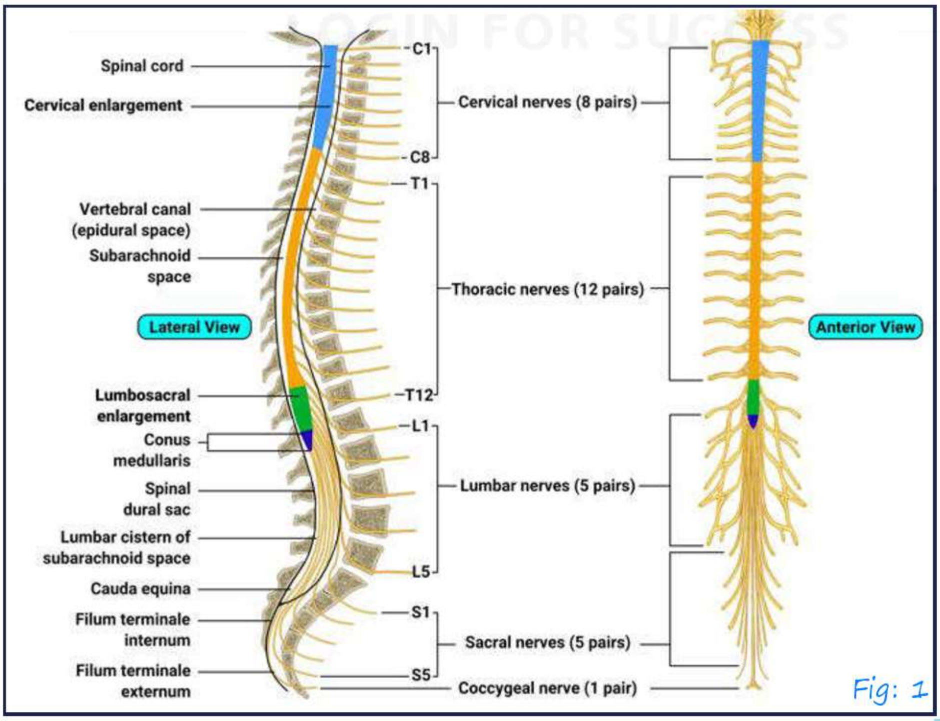

Fig: 1

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- 31 pairs of spinal nerves and spinal segments
- Spinal Nerves
  - 8 pairs of cervical
  - 12 pairs of thoracic
  - 5 pairs of lumbar
  - 5 pairs of sacral
  - 5 pairs of coccygeal
- 33 Vertebra
  - Cervical-7
  - Thoracic-12
  - Lumbar-5
  - Sacral- 4
  - Coccygeal-4
- All the spinal segments have ended in conus medullaris (L1)
- All these rootlets from l1 lie in lumbar cistern

  → lower part of spinal cord

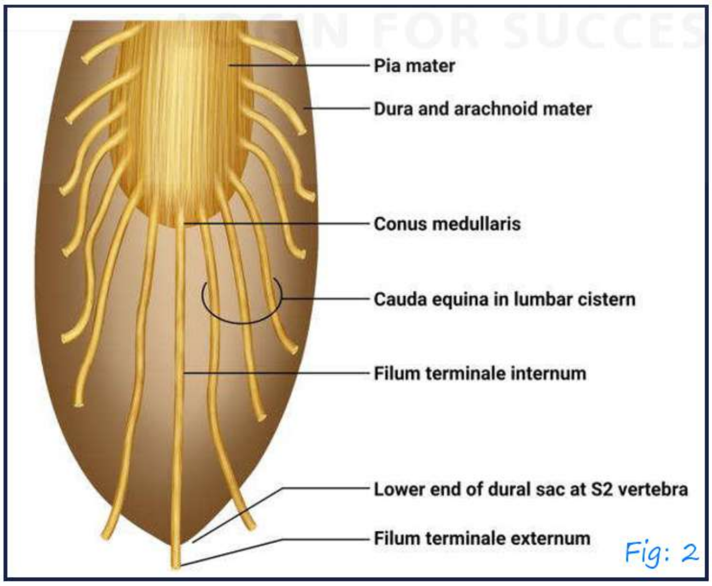

Fig: 2

- Conus lesion-UMN lesion
- Caudus lesion-LMN lesion

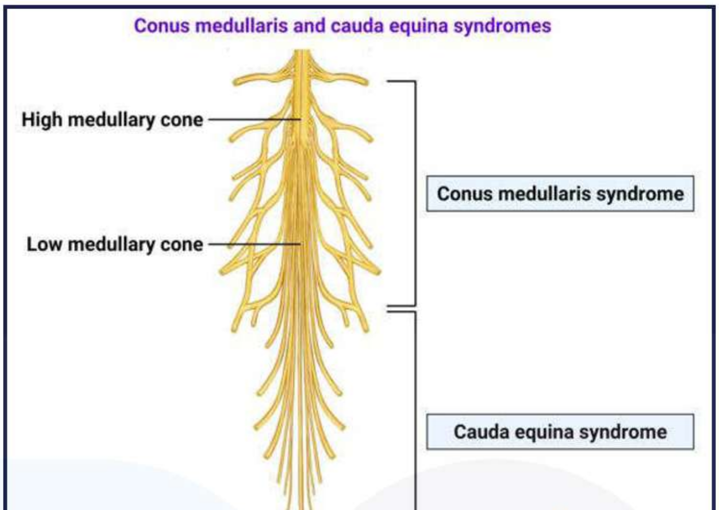

Fig: 3

- Conus medullaris – [conus (s3, s4, s5, spinal segments)
  Epic onus (L4, l5 s1, s2)

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CONUS LESION	CAUDA WQUIVA LESION
UMN LESION	LMN lesion (ventral root
S1, S4, S5, spinal segments	L1 and below roots
motor: - No motor defects exception→ epic onus involved Reflexes N expect epic onus involvement	LMN type of weakness ↓ areflexia ankle jerk (s1, s2a) absent' knee jerk (L2, L3, L4) absent
sensory Perianal sensation (Saddle region) image25:59 B/L symmetric saddle anesthesia	Radicular pain (root pain) ↓ electric shock like pain ↓ asymmetric saddle anesthesia
Bowel &bladder LMN bladder Early bladder involvement	LMN bladder LMN bladder involvement

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- Lower motor neuron consists of anterior horn cell. Ventral root, ventral rami(root), brachial plexus/lumbo-sacral plexus, peripheral nerves, neuromuscular junction2 musle

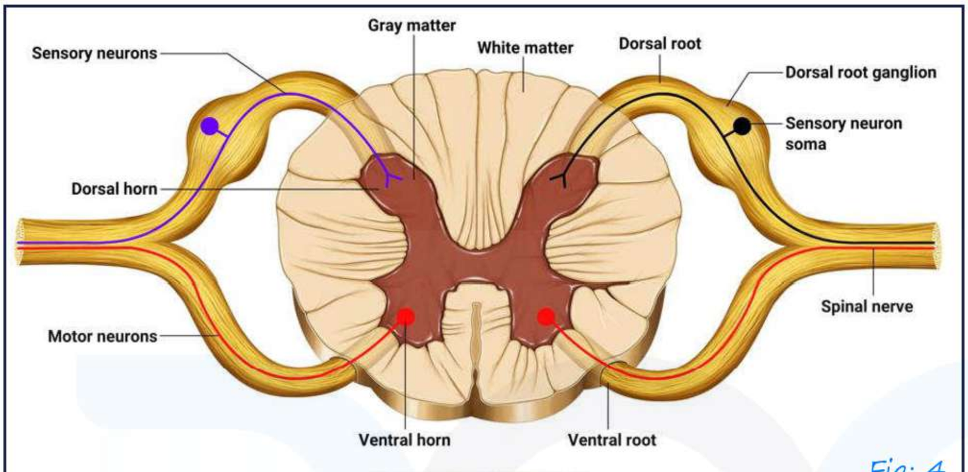

Fig: 4

- Any asymmetric sensorimotor involvement of lower limbs unless until proved is cauda equina syndrome
- Conus lesion- Ependymoma
- Caudus lesion- Disc bulge
- White motor of spinal cord-highway

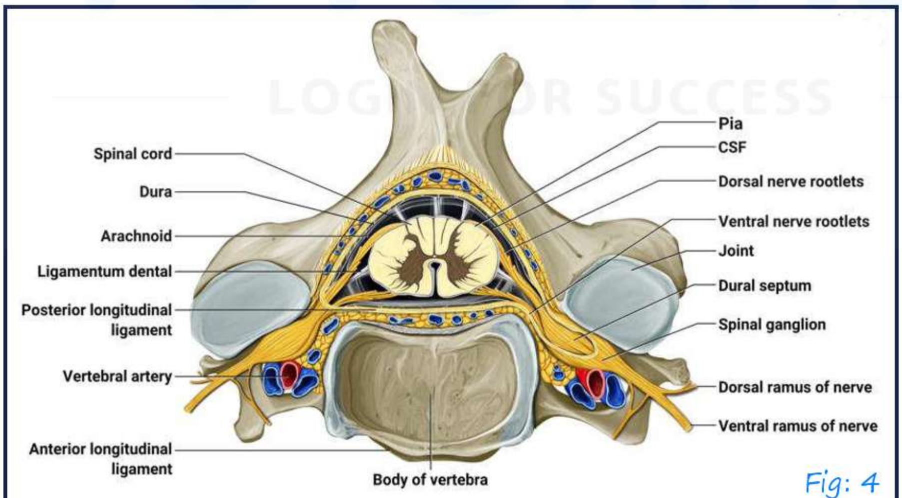

Fig: 4

- Commonest disc bulge-posterolateral disc bulge
  - Lateral view of cervical region

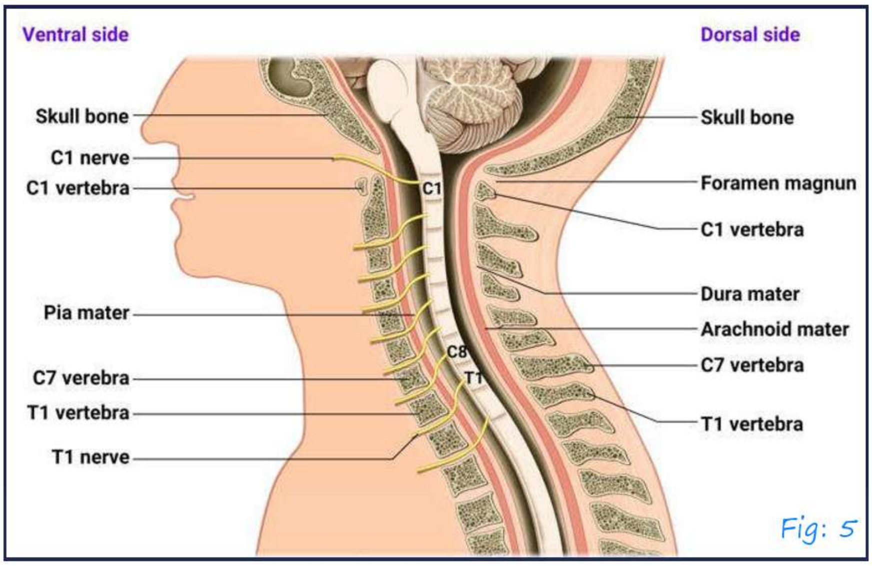

Fig: 5

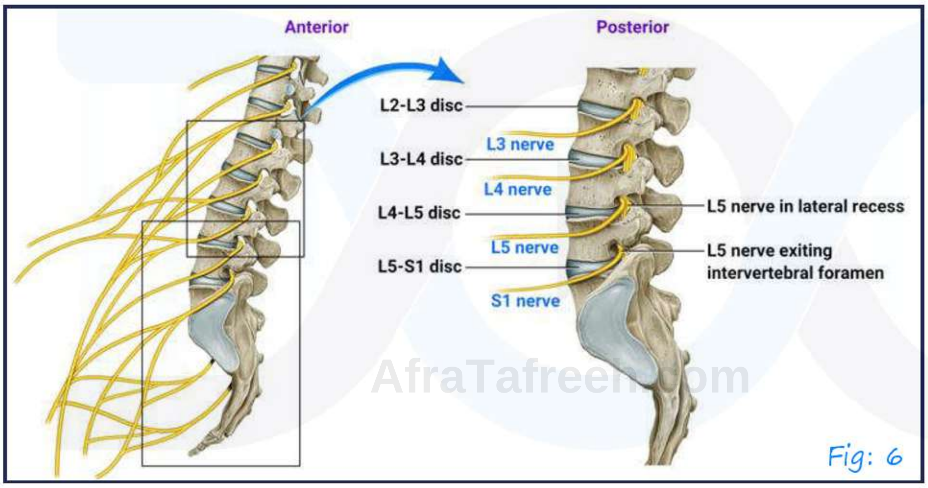

Fig: 6

- L5-s1 disc bulge→ S1 is affected

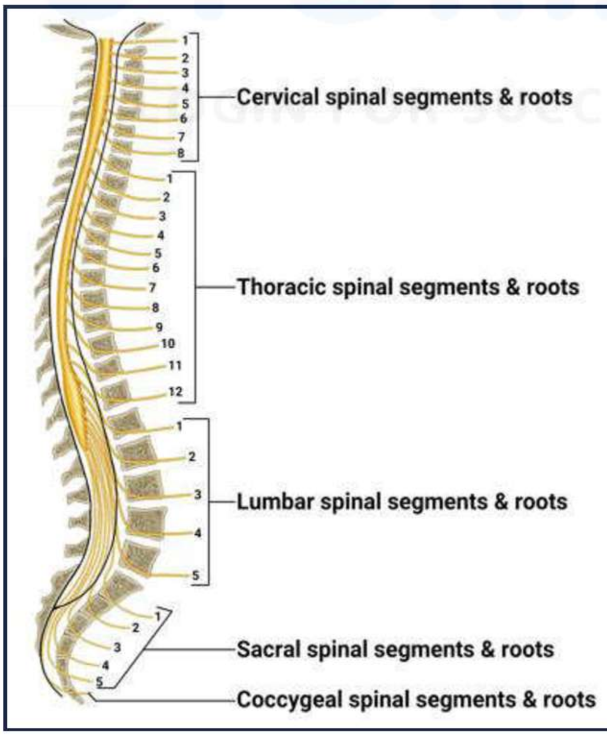

Fig: 7

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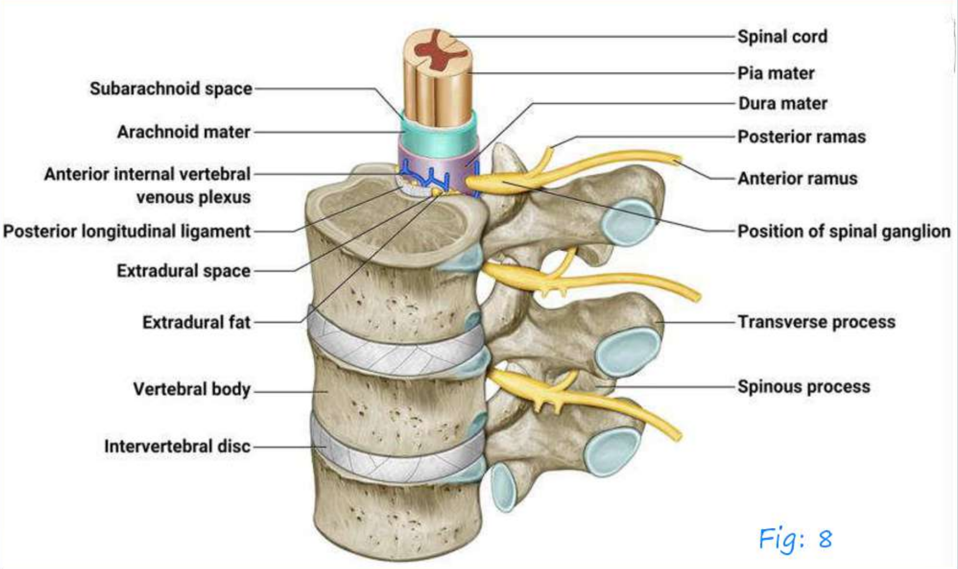

Fig: 8

→ spinal segments and Vertebral

Regions	Spinal segments	Vertebral level	General rule
Upper cervical	C2	C2	Same level
Lower cervical	C6	C5	One vertebra above
Upper thoracic	T5	T3	Two vertebrae above
Lower thoracic	T10	T7	Three vertebrae above
Lumbar	L1-l5	T10-t11	Three to five vertebrae above
Sacral and coccygeal	S1-S5 and Cx1	T12-L1	Six to ten vertebrae above

Spinal Tracts 00:47:36

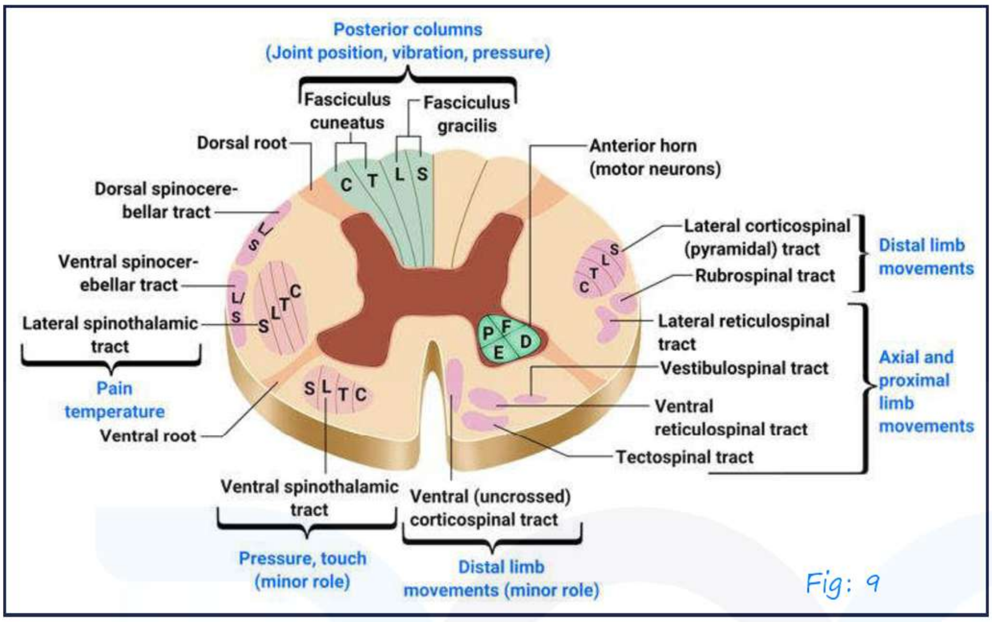

Fig: 9

- Gray mater – Anterior horn → LMN weakness corresponding
  Affected to spinal segments

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White mater

- Motor
  - Extrapyramidal tracts
  - Pyramidal tracts

Pyramidal

- Lateral corticospinal (pyramidal) tract

  ↓

  X for fine skilled movement involving distal limbs

- Ventral corticospinal tracts

  ↓

  Power of axial muscles

Extrapyramidal

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- Rubrospinal tract
- Lateral reticulospinal tract
- Vestibulospinal tract
- Ventral reticulospinal
- Dorsal reticulospinal
- Tecta spinal

Sensory Pathways

- Carried out by- spinothalamic tract
  Dorsal column pathway
- Spinothalamic tract
  - Lateral → pain & temperature
  - Anterior →touch (crude touch)
- Dorsal column pathway → Fine touch
  Vibration
  Proportion
  Joint Position sense

Pathways 00:53:38

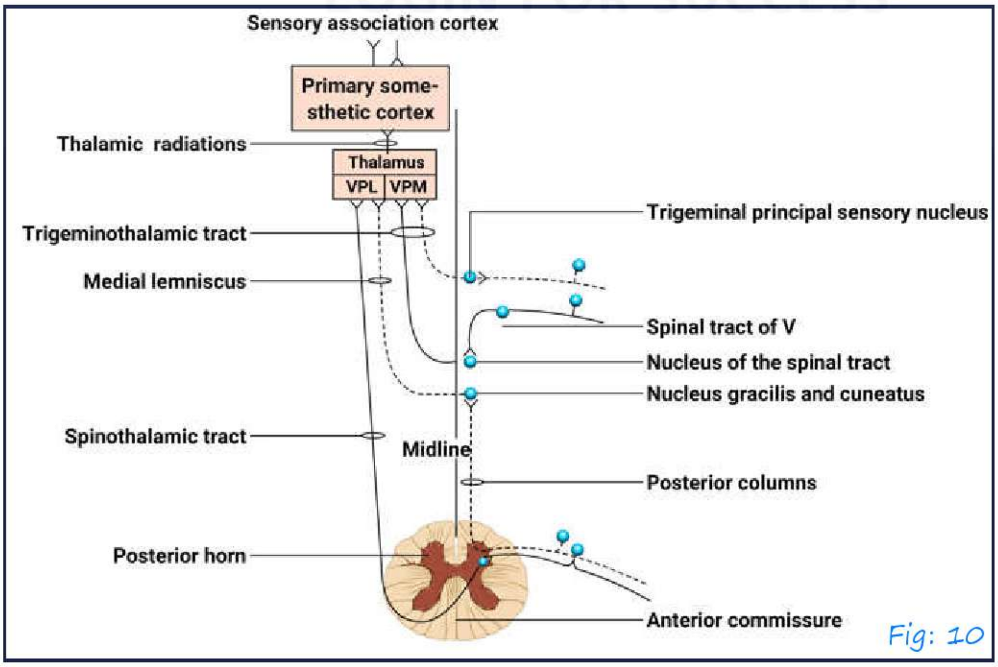

Fig: 10

- Spinothalamic tract crosses at the level of spinal cord
- First order neurons go up along the posterior column that is Fasciculus gracilis cuneatus, reach the region of medulla and Then cross to opposite side and ascend and medial lemniscus
- Spinothalamic tract and medial lemniscus ascend and synapse at nucleus of ventral posterolateral nucleus of thalamus
- From VPL, 3rd order neurons relate to the sensory complex
- Trigeminothalmic tract→carries sensation from face
- Trigeminothalamic tract also known as Quintothalamic tract
- Trigeminithalamic tract synapses at ventral posteromedial Nucleus of thalamus

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Blood Supply of Spinal Cord 00:57:46

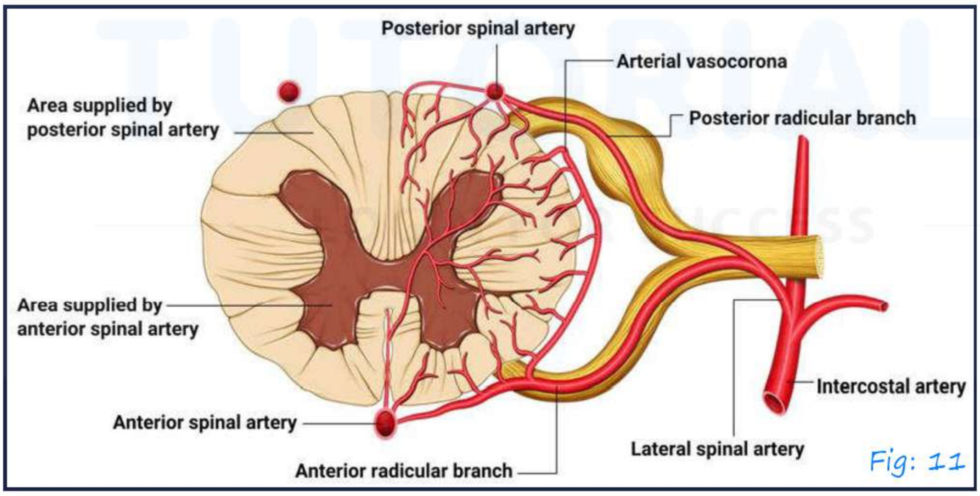

Fig: 11

- Ant 2/3 – ant. Spinal artery
- Post 1/3 – Posterior spinal artery
- Artery of Adamkiewicz – large radicular artery which reinforces the blood
- Supply of spinal cord.

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SPINAL CORD SYNDROMES

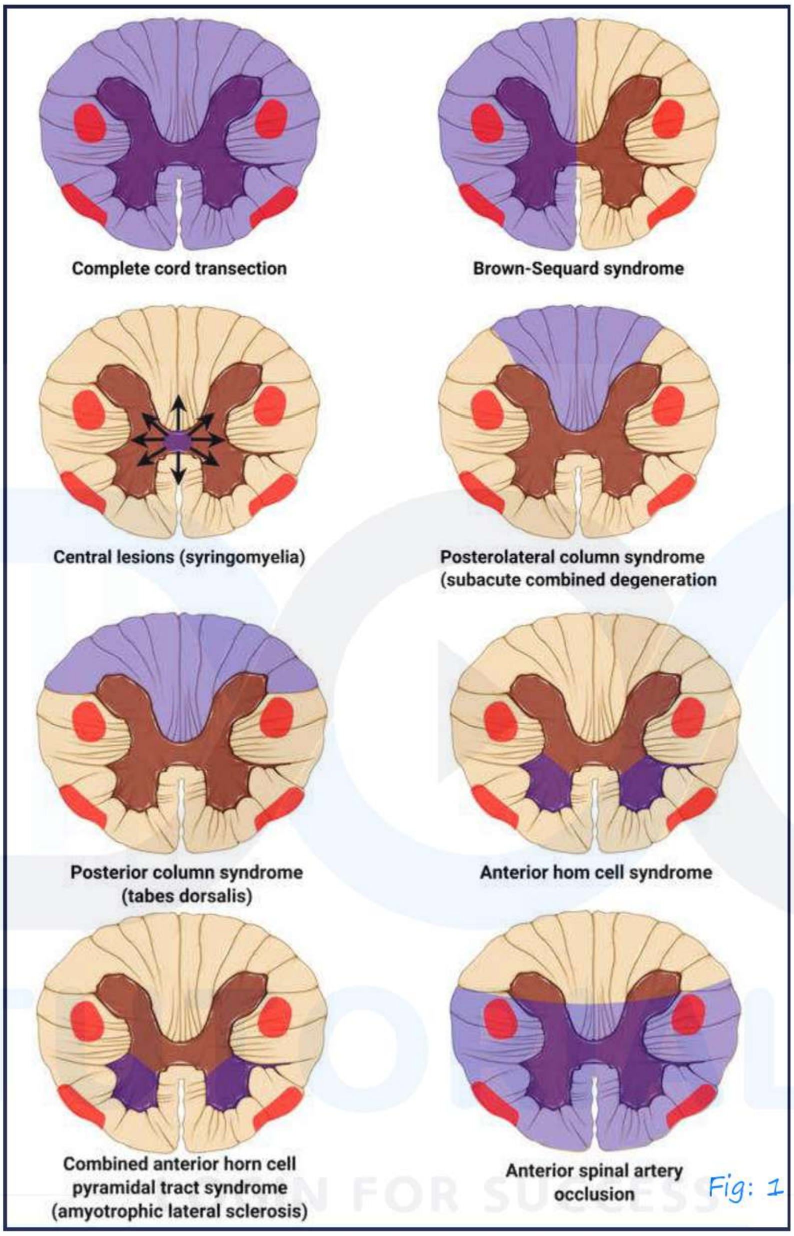

Fig: 1

Complete Cord Transection 00:00:56

- RTA- B/L affection of gray and white matter.

↓

Motor problems

Sensory problems

Bladder problems

- High lesion in cervical cord→quadriplegia

- Lower lesion in cervical cord→ paraplegia
- Affects posterior column and spinothalamic tract Bilaterally

Brown -Sequard Syndrome 00:03:15

- Hemi section of spinal cord

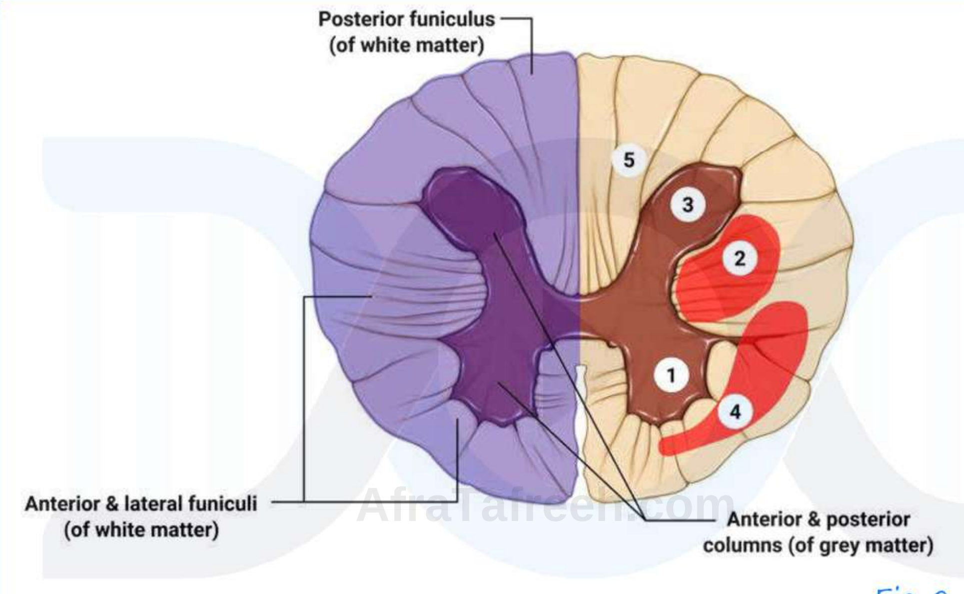

Fig: 2

- U/L affection of gray and white matter

↓

Motor &sensory pathways affected

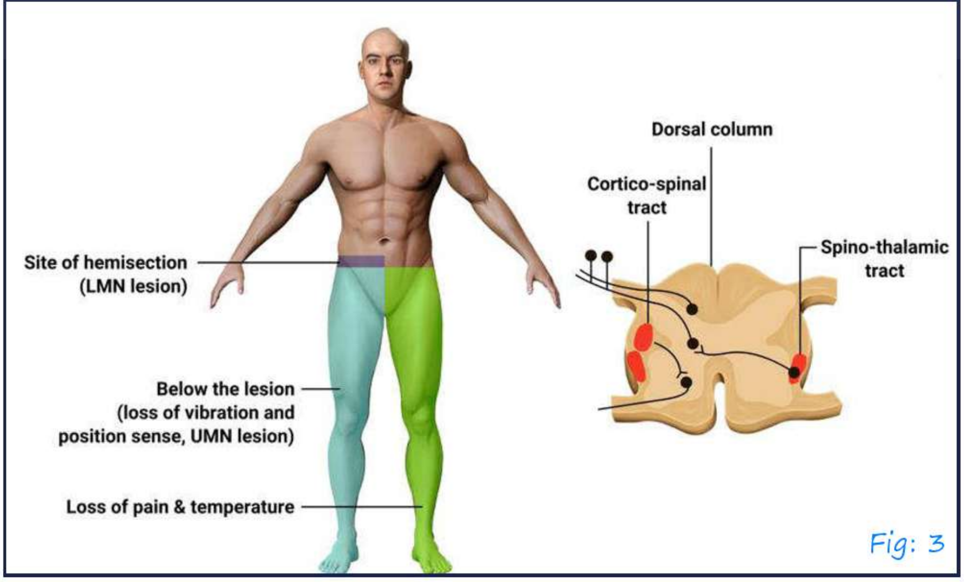

Fig: 3

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- At the level of section→ LMN pattern of weakness

↓

Involvement of anterior horn

Cells

- Crossing of spinothalamic tract is not at the same level
- When ascending, it ascends up 2 spinal segments &then crosses

  To opposite region

- Lesion of spinothalamic tract would cause sensory affection of corresponding region

  ↓

  Weakness and small segmental region loss of pain and temperature of same side

- Since, the whole white matter is involved → Pyramidal weakness
- R conditional tract is involved

  ↓

  R sided UMN weakness

- R posterior column pathway affected

  ↓

  R fine touch
  Joint position sensation
  Vibration
  } affected

  Proprioception

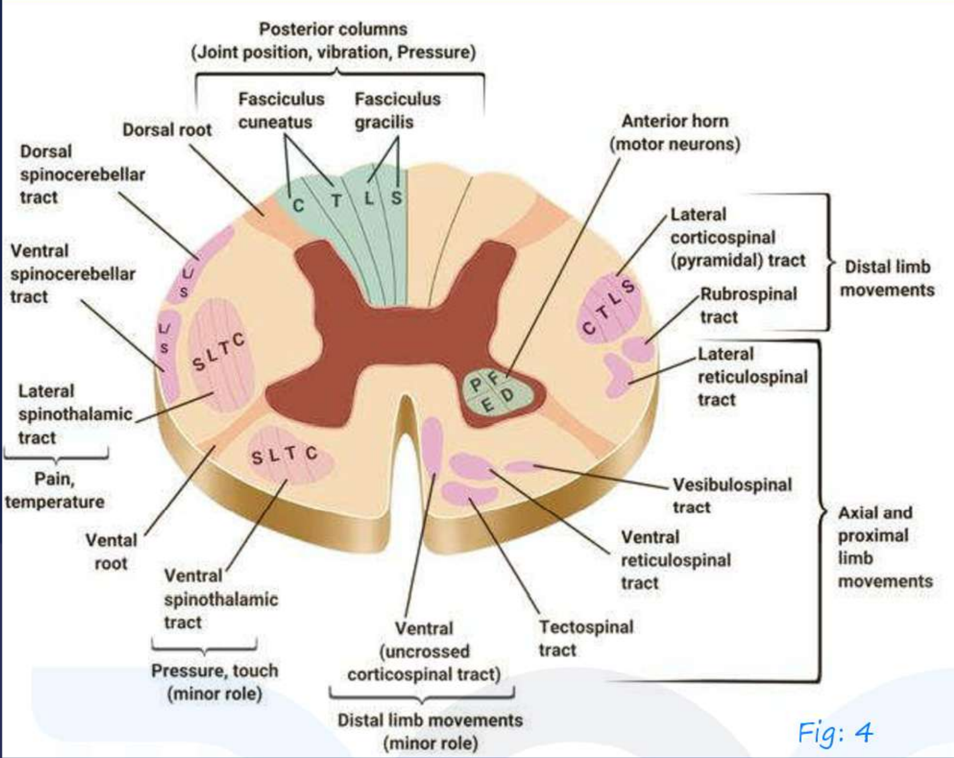


Fig: 4

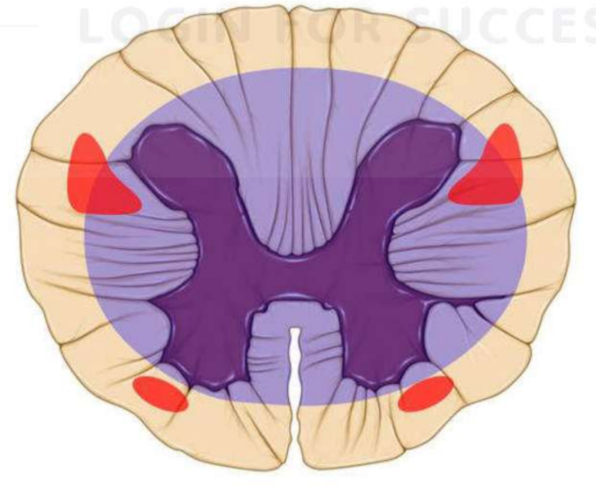
- Spinothalamic tract affected

↓

Loss of pain and temperature on opposite side

Central Cord Syndrome 00:10:51

Syringomyelia


Central Cord Syndrome Fig: 5

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- Syrinx → cavity filled with CSF
  - → Located centrally
  - →Expands and involved cord→ syringomyelia
- Syringomyelia- prototype of central cord syndrome
- Commonest site of syringomyelia – cervical spinal cord
- Syrinx extends into medullary region- synnglobulbia

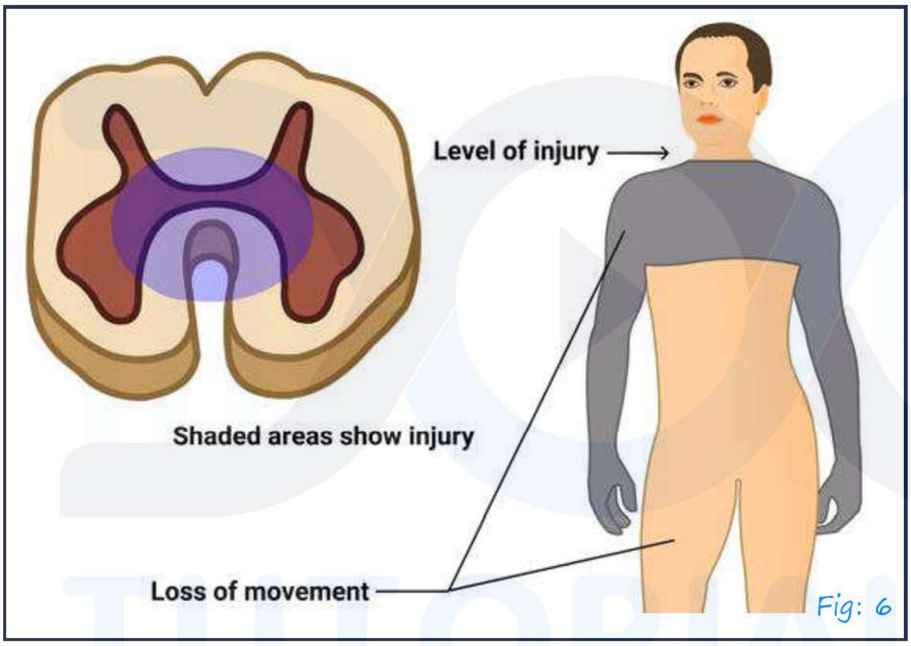

Fig: 6

- Manifestation
  - Sensory → crossing of spinothalamic tract affected

    ↓

  - B/L loss of pain and temperature
  - Sparing of posterior column
  - Dissociated sensory loss
  - Motor→ LMN segmental weakness
  - Corticospinal pathway involved → pyramidal weakness

    Below (UMN lesion)

- Preferentially involved cervical fibers first

↓

Dissociates suspended sensory loss

→ T2 sagittal view

Fig: 7

- Syringomyelia often associated Arnold Chiari malformation type I

↓

Look for tonsillar decent

- Syringomyelia – presents with painless burns
- Distribution of syringomyelia -cape like distribution
- Syrinx extends into medullary region- distribution of sensory loss
  - complete cord transection

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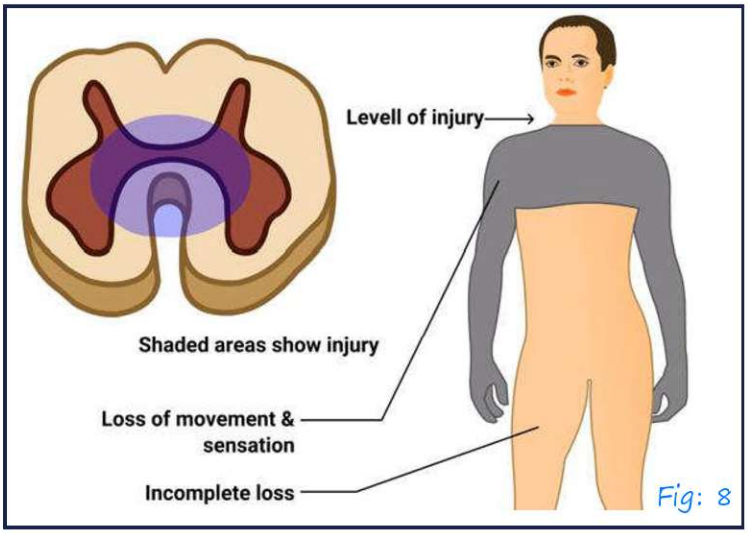

Fig: 8

Posterolateral Column Syndrome 00:23:32

- SACD due to vitamin b12 deficiency

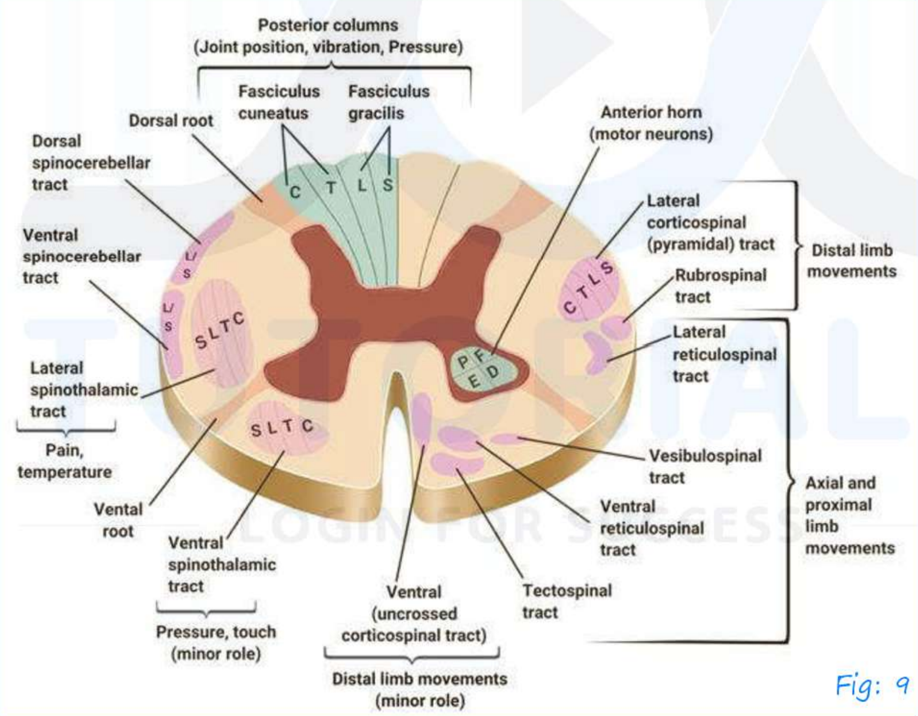

Fig: 9

- Sensory problems are predominantly posterior column sensations
- SACD – pyramidal features

  B/L

  B/L extensor plantar

Peripheral neuropathy

↓

Coexisting with vitamin B12 deficiency → ankle jerk

Posterior Column Syndrome 00:26:28

- Neurosyphilis → posterior column & dorsal root ganglia

↓

Ataxia + areflexia

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Anterior Horn Cell Syndrome 00:27:17

- Motor neuron disease
- ALS → combined anterior horn cell- pyramidal tract Syndrome

Anterior Spinal Artery Occlusion 00:28:01

- Involvement of B/L anterior 2/3 rd. of spinal cord
- Affects both corticospinal tract and spinothalamic tract
- Rarely posterior spinal artery occlusion where only Posterior column fibers are affected

Higher Cervical Cord Lesions 00:31:21

- Involves segments C3, C4, C5 → phrenic nerve

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Foramen Magnum Syndrome 00:31:21

- pattern of weakness: – I/L UL, I/L LL, C/L LL, C/L LL – 'U' pattern of weakness
- Also referred to as E/s berg phenomenon

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CLASSIFICATION OF MYELOPATHIES

Classification of myelopathies 00:00:10

Classification of myelopathies

- Compressive
  - Intradural
    - Intra-medullary
    - extra – medullary
  - extradural
- non compressive

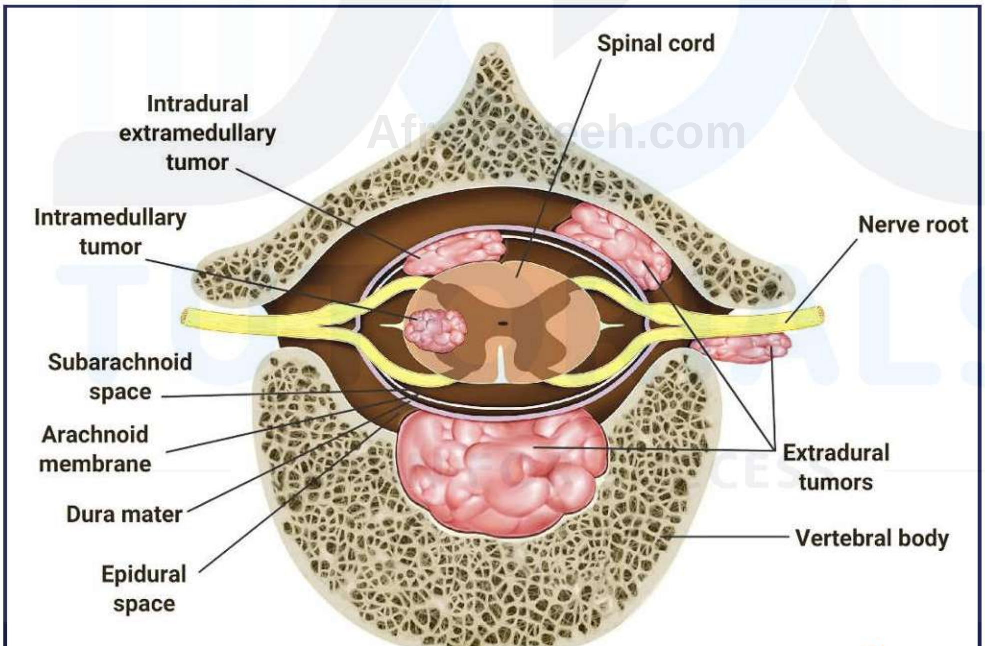

Fig: 1

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Extramedullary extradural	Extramedullary intradural	Intramedullary
Cervical spondylosis	Meningioma	Syringomyelia
IVDP	Neurofibroma	Ependymoma
TB spine	Arachnoiditis	Glioma
Metastasis	AV malformations	
Epidural abscess, hematoma		

Features	Extramedullary	Intramedullary
Pain	Radicular pain	Funicular pain
Vertebral pain	Common	Uncommon
Sacral Sensations	Lost	Sparing
Dissociated Sensory loss	Absent	Present
Paraesthesias	Ascending	Descending
Corticospinal Tract	Early	Late
Bladder	Late	Early
CSF proteins	Raised	Normal

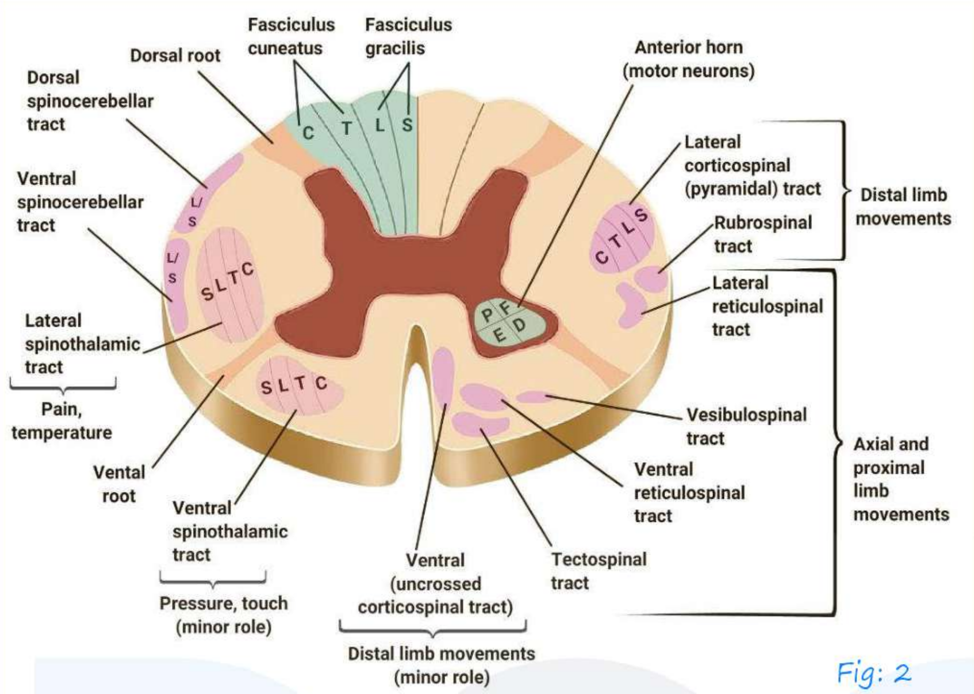

Fig: 2

Non compressive myelopathy

NONCOMPRESSIVE MYELOPATHIES
• Demyelinating (e.g., TS, ADEM) • Hereditary (e.g., spastic paraplegia) • Viral myelitis (e.g., varicella-zoster, AIDS-related myelopathy human T-lymphotropic virus type I infection) • Syringomyelia • Vitamin B12 deficiency and other nutritional deficiencies Infarction • Ischemia and hemorrhage from vascular malformations or • cavernoma • Spirochetal diseases (syphilis and Lyme disease) • Toxic myelopathies (e.g., radiation-induced) • Autoimmune diseases (e.g., lupus, Sjögren syndrome) • Paraneoplastic • Neuronal degenerations • Tethered cord at the cauda equina • Acute and subacute transverse myelitis of unknown cause

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Transverse myelitis 00:12:50

- Acute or subacute inflammatory disorder involving spinal cord
  - Infection
  - Multiple sclerosis, neuromyelitis optica
  - Vaccination.

Diagnostic Criteria for Transverse Myelitis.
• Sensory, motor or autonomic dysfunction attributable to the spinal cord • Bilateral signs and/or symptoms • Clearly define sensory level • No evidence of compressive cord lesion • Inflammation defines by cerebrospinal fluid pleocytosis or elevated IgG index or gadolinium enhancement • Progression to nadir between fours and 21 days

- In compressive myelopathy, sensory level would be there

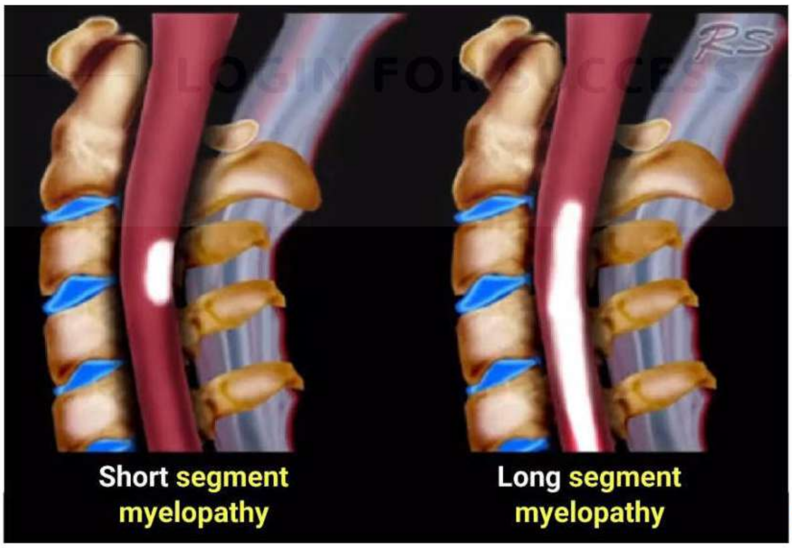

Fig: 3

- Long segment myelopathy

  - LETM
- Longitudinally extensive

  Transverse myelitis
- Favors NMO spectrum disorder
- Treatment of transverse myelitis

  Acute: - i. V methyl prednisolone 1g x 5 days.

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NEUROGENIC BLADDER

Introduction 00:00:18

- Detrusor muscle
- Internal urethral sphincter
- External urethral sphincter.

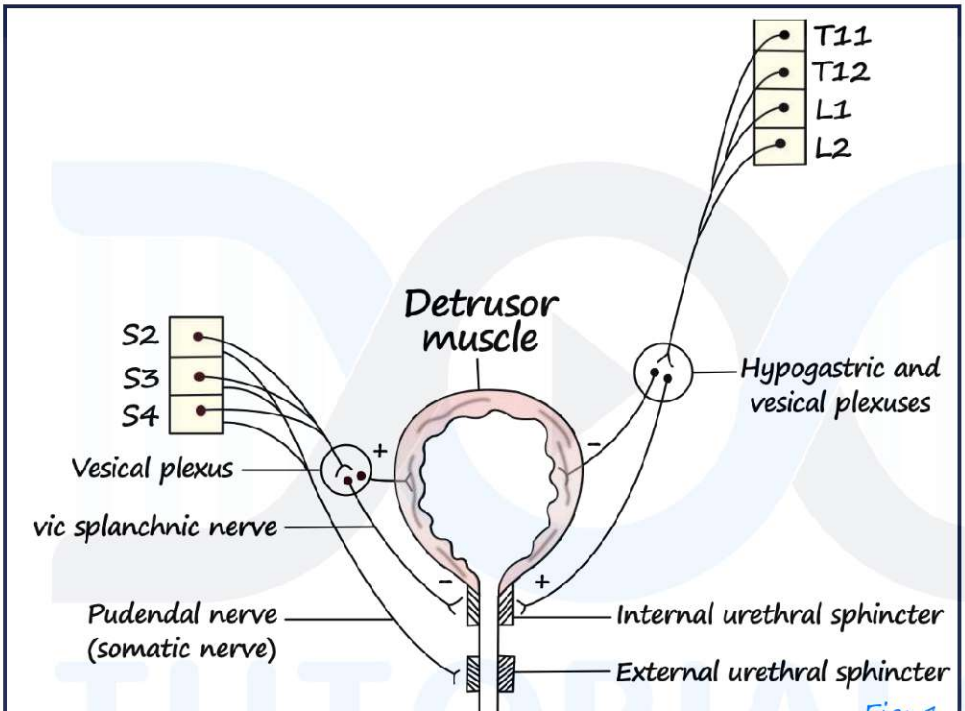

Fig: 1

Innervation of bladder

- Sympathetic
- Parasympathetic
- Somatic

Sympathetic supply 00:02:26

Sympathetic supply (filling nerve)

- $T_{11} - L_2$
  - Intermediolateral horn

- Supplies
- Bladder wall (β_3 receptor)
- Internal urethral sphincter (α receptor)
- Causes relaxation of detrusor muscle and contraction of internal urethral sphincter → filling phase
- Inhibition of parasympathetics

Parasympathetic supply 00:05:40

Parasympathetic supply (Nerve of urination)

- S_2, S_3, S_4 } Intermediolateral horn
- Predominantly innervates detrusor muscle

↓

Contains Ach-muscarinic receptors M_2, M_3

↓

Detrusor contraction

Somatic supply 00:07:30

- S_2, S_3, S_4 } onuf's nucleus
- Supply external urethral sphincter

↓

Contains Ach – nicotinic receptor

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Bladder
- Storage phase
- voiding phase

Neurogenic bladder disorders 00:09:20

- Pons – Barrington nucleus
  - For initiating micturition
- Supra-pontine control
  - Paracentral lobule
  - Cingulate cortex
  - Insular cortex
  - Periaqueductal gray
- Suprapontine

  ↓ (-)
- Barrington nucleus
- Two tracts responsible
  - Reticulospinal tract → facilitates micturition
  - Corticospinal tract → inhibits micturition
- Bladder has viscoelastic properties

  ↓

  When urine gets filled, bladder wall expanded and impulses go up the spinal cord by means of spinothalamic tract and posterior column

  ↓

  Carried by AS fibers

Neurogenic bladder

1. Uninhibited bladder/cortical bladder
   - No problem in sympathetic /parasympathetic supply
   - Known as safe bladder
2. S_2, S_3, S_4 segments involved

↓

Depends on autonomic reflexes to empty

↓

Autonomous LMN bladder

↓

Voiding problems

↓

Retention

Poor stream

Interrupted stream

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3. Suprasacral infrapontine
   - Automatic UMN bladder → reflex neurogenic bladder
   - Voiding and storage problem → urge incontinence
     Increase urinary frequency
     urgency
   - Voiding problem is due to detrusor sphincter dyssynergia
   - Small volume accumulation → increase urgency
   - Spastic UMN bladder

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4.Affection of sensory root

↓

Sensory paralytic bladder

↓

Occurs in tabes dorsalis

5.Motor paralytic bladder

- Bulbocavernosus reflex and anal reflex → absent in LMN bladder.

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CHECKLIST IN A CASE OF PARAPLEGIA QUADRIPLEGIA

Site of lesion 00:01:40

- Site of lesion: - cortex

  Brain stem

  Spinal cord

  Roots

  Peripheral nerves — GBS (Roots, Peripheral nerves, MMJ)

  MMJ

  Muscles

- Cortex → SSS thrombosis.
- Brain stem -> Basilar artery stroke
- Spinal cord
  - Compressive
  - Non compressive
- NMJ – myasthenia gravis
- Muscle- Inflammatory myopathy
- Age of patient
- Onset and progression

Acute	sub-acute	chronic
ATM	spinal cord tumor	HSP
GBS	spinal	ALS
	epidural	
	absence	

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Motor symptoms 00:06:40

- UMN/LMN
- Stiffness
- Dragging

(Stiffness, Dragging → UMN)

- Cristal - UMN
- Proxima-LMN
- Hypertonia
- Brisk OTR
- Extensor plantar

(Hypertonia, Brisk OTR, Extensor plantar → UMN)

- Hypertonia
- Absent/decrease OYR
- Flexor plantar

(Hypertonia, Absent/decrease OYR, Flexor plantar → LMN)

- Pyramidal distribution of weakness- UMN
- UL- extensors will be more week
- LL- flexors will be more week

Sensory Symptoms

- Root pain→ Important localizing value
- Fascicular pain → intramedullary lesions

  Poor localizing value
- Vertebral pain → localizing value

  Pott's spine
- Girdle sensation → posterior column involvement

  → poor localizing value

Sensory symptoms

Positive → Burning, Lancinating

Negative → numbers, pins& needle sensation

- Look for definite sensory level

Bladder

- Intramedullary lesion → bladder involvement

Compressive Myelopathy

- Identify the motor level
- Reflex level
- Sensory level
- Vertebral level
- T4- Nipple
- T6- xiphisternum
- T10 – umbilicus
- Segmental innervations of abdomen are from t6-t12

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Fig: 1

Bevor's SIGN: -

- Patient is lying supine and ask the patient to flex his neck

  ↓

  Upper abdominal muscles contract and pull umbilicus

  Upwards

  ↓

  Positive Bevor's sign

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CARDIOMYOPATHIES

Cardiomyopathy 00:00:31

- Cardiomyopathy – Defined as morphological or a functional affection of myocardium
- Exclude
  - CAD
  - Valvular heart disease
  - Severe HTN
- American heart association classification
  ↓
  i. Primary
  ii. Secondary
- European society of cardiology classification
  ↓
  i. Dilated cardiomyopathy
  ii. Hypertrophic cardiomyopathy
  iii. Restrictive cardiomyopathy
  iv. Arrhythmogenic right ventricular cardiomyopathy (ARVC/ARVD)
  v. Unclassified
     - LVNC
       ↓
       Left ventricular non compaction
     - Takotsubo cardiomyopathy

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Dilated cardiomyopathy 00:07:54

- Characterized by ventricular dilation (L>R)

  ↓

  often biventricular

  - Thinning of myocardial wall
  - Dilation of cardiac chambers
- Global dilation
- Flabby, dilated and globular heart
- Prevalence – 1 in 2500

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Etiology 00:12:38

- Genetic causes
  - 30% familial
  - TTN mutation (titin) → most common gene mutation
  - Lamin A/C gene
  - Duchenne muscular dystrophy/Becker
  - Emery Dreifuss
- Idiopathic
- Specific causes

  i. Inflammatory (myocarditis) → Infective

  ↓

  a. parvovirus

  b. Coxsackie

  c. HIV

  d. Hep C

  e. Adenovirus

f. HHV-6

g. Diphtheria

h. B. burgdorferi – Lyme disease

i. Chaga's disease – T. cruzi

j. Covid-19

- Non infectious

↓

a. Sarcoidosis

b. Polymyositis

c. Dermatomyositis

d. Giant cell myocarditis

ii. Toxins & drug induced

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a. Alcohol (most common toxin)

b. Hydroxychloroquine

c. Interferon

d. Anthracyclines (Doxorubicin)

e. Transtuzumab

f. Lead, mercury

g. Anabolic steroids

iii. Nutritional causes

↓

a. Thiamine def

b. Selenium def

iv. Endocrine

a. Pheochromocytoma

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b. Hypo/hyperthyroidism

c. Diabetes

v. Hemochromatosis → most common clinical presentation

↓

dilated cardiomyopathy

vi. Electrolyte disorders

a. Hypocalcemia

b. Hypophosphatemia

vii. Peripartum cardiomyopathy

- Last trimester of pregnancy – 6 months post-partum
- Risk factors
  - Increased age
  - Increased parity
  - Multiple pregnancy
  - Malnutrition
  - Tocolytics in pre-term labor
  - Pre-eclampsia
- Good prognosis

Fig: 1

Clinical features 00:31:08

- Clinical features – systolic heart failure > diastolic
  - Exertional dyspnea
  - Orthopnea
  - PND
  - Palpitations
  - As the disease progress → patient has dyspnea @ rest
  - Pulmonary edema
  - Pedal edema
  - Ascites
- Sudden cardiac death because of arrhythmias
  ↓
  - AF
  - VF/Ventricular tachycardia

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Examination findings 00:36:01

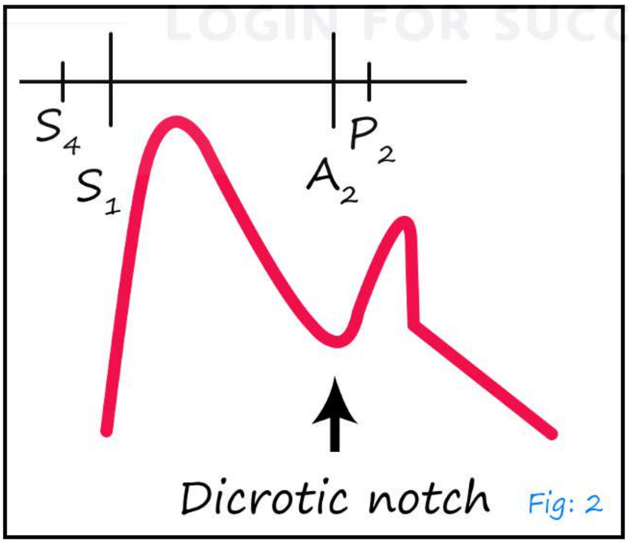

Fig: 2

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- Twice beating pulse one peak systole, next peak diastole – Dicrotic pulse
- Hypokinetic, diffuse apex beat
- Pan systolic murmur associated with MR, TR
- Soft S_1
- S_3 ⊕
- Bibasal crepitations
- Arrhythmias

Investigations 00:38:30

- IOC – Transthoracic echo (TTE)

  ↓

  - Systolic dysfunction
  - Enlarged cardiac chambers
  - MR, TR
  - Pulmonary HTN
  - Intramural thrombus

  Echo → helps to rule out 2° causes
- If cardiac MRI in options → best IOC
- CXR – cardiomegaly

  Increases CT ratio
- ECG – Non specific ST-T changes

  Atrial enlargement

  LBBB> RBBB

  septal Q waves
- Endomyocardial biopsy – may be of utility in
  - Myocarditis

- Amyloidosis
- Hemochromatosis
- Sarcoidosis

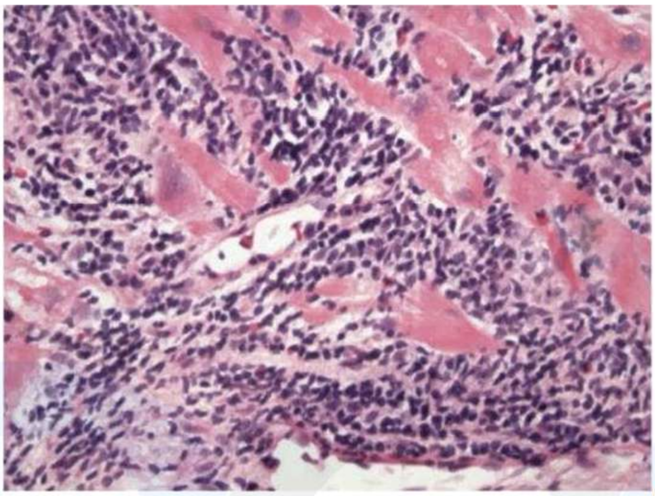

Fig: 3

Myocarditis-Sheets of inflammatory cells

- Dalla's criteria – Histopathological categorization of myocarditis

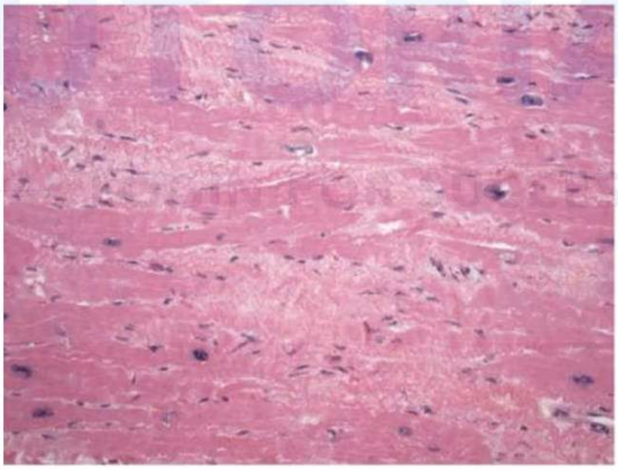

Fig: 4

- Myocyte damage
- Nonspecific interstitial fibrosis
- Enlarged nuclei.

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Treatment 00:48:27

Treatment

Symptomatic
- Loop diuretics
- Salt restriction
- Digoxin

Prolong survival

i. β blockers – Bisoprolol
   - Carvedilol
   - Sustained release metoprolol

ii. ACE inhibitors/ARB's

iii. Aldosterone antagonist
   - spironolactone

iv. Sacubitril + valsartan
   ↓
   Neprilysin inhibitors

- If the patient has LVEF <30%
  (or)
  H/O prior cardiac arrest
  (or)
  Ventricular fibrillation
  (or)
  Sustained ventricular tachycardia

  → Implantable cardiac device (ICD)
- If EF <30% + LBBB → Cardiac Resynchronization therapy (CRT)
- DCM – one of the indications for heart transplantation.

HYPERTROPHIC CARDIOMYOPATHY

Introduction 00:00:22

- Most common genetic cardiac abnormality
- Prevalence 1:500
- Most common cause of sudden death in young adults
- Predominantly genetic
- Autosomal dominant
- Mutation in sarcomere gene

↓

- Most common **MYH 7 gene**(Beta myosin heavy chain)
- My BPC3 (Myosin binding protein)

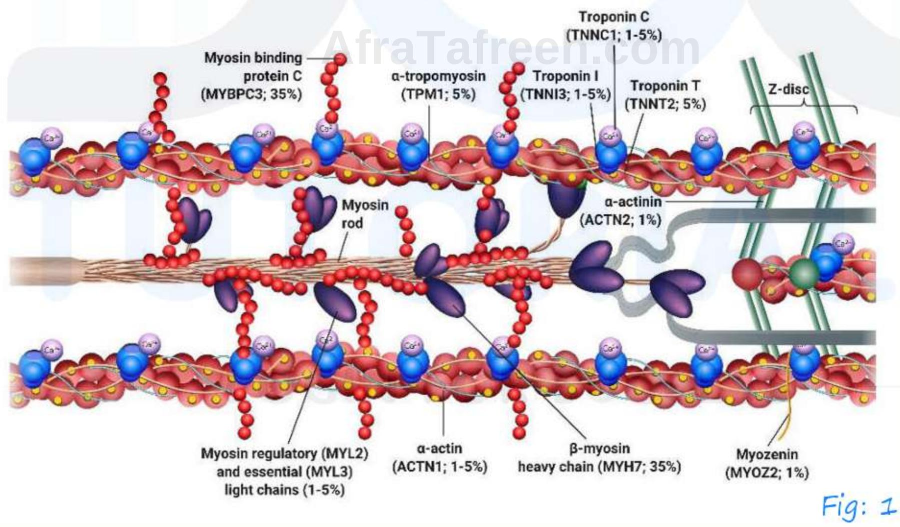

Fig: 1

- Charactered by Hypertrophy of ventricles (LV >>>RV)

↓

Should be absence / disproportionate to hemodynamic factors like

- HTN
- Aortic valve disease

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– Infiltrative/Storage disorders

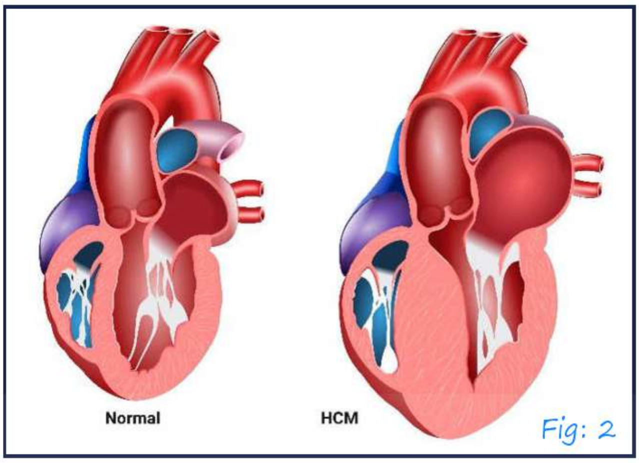

Fig: 2

Abnormalities

- Asymmetric septal hypertrophy – mc
- Hypertrophy of LV free wall
- (septal hypertrophy >> Free wall)
- ↓↓↓ LV cavity size
- In hypertrophic cardiomyopathy, there occurs dynamic LVOTO →left ventricular outflow tract obstruction
- SAM –Systolic anterior motion of anterior mitral leaflet(cause dynamic LVOTO)
- Other names of hypertrophic cardiomyopathy
- ASH (Asymmetric Septal hypertrophy)
- IHSS (Idiopathic hypertrophic subaortic stenosis)
- HOCM (Hypertrophic obstructive cardiomyopathy)

  → Not used now

Fig: 3

- complete myocyte disarray
- criss cross arrangement of muscle fibres
- interstitial fibrosis

Clinical Features   00:23:10

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- Clinical features: mainly due to dynamic LVOTO
- Diastolic failure (hallmark)

    1. Asymptomatic

    2. Symptoms if present in Adolescence / Young adults

    3. M=F

- Dyspnoea on exertion (due to pulmonary edema)
- Exercise intolerance
- Fatigue
- Palpitations
- Anginal episodes → ↓EDV, ↓ CO, ↓coronary perfusion } Ischemia

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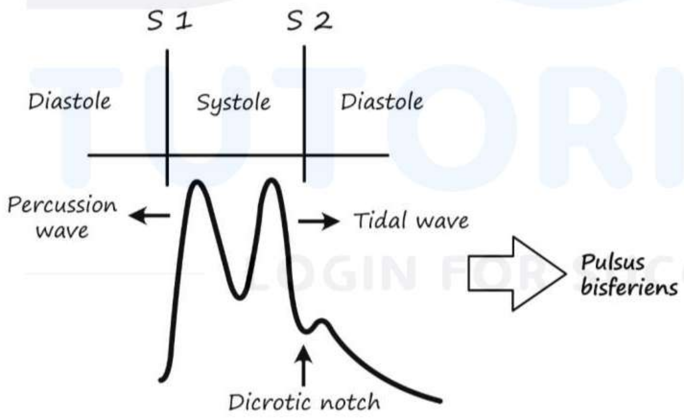
- ↑↑ Demand & ↓ supply → Subendocardial ischemia
- Certain coronary microvascular changes → anginal episodes
- Pre syncopal / syncope
- Due to LVOTO - Arrhythmias - Ventricular tachycardia
  Ventricular fibrillation
- Sudden cardiac death
- Most common sustained arrhythmia in Hcm - Atrial fibrillation
- Positive family history

Examination findings 00:36:01

1.Pulse - Pulsus bisferiens - 2 peaks in systolic



2.Apex - double apex beat

3.Heart sounds - S2 split narrow
↓
Single S2
↓
reverse split
S4

4.Ejection systolic murmur over aortic region

- ↑ in intensity in ↓Pre-load ↓After load ↑ myocardial Contractility.] ↑↑ LVOTO, ↑↑ Intensity murmur, ↑↑ severity of symptoms
- Decrease Pre load
  - Valsalva
  - Standing
  - Nitrates
  - Diuretics
  - ACE inhibitors
- Decrease after load → Amlodipine
- Increase myocardial contractility →Digoxin

  So all these drugs should be avoided.
- Sometimes association with SAM - mitral regurgitation (+) Pan systolic murmur over apex

Investigations 00:45:54

1.TTE

- Diastolic dysfunction
- Asymmetric septal hypertrophy
- SAM

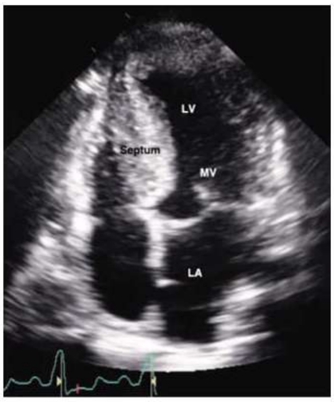


Fig: 4

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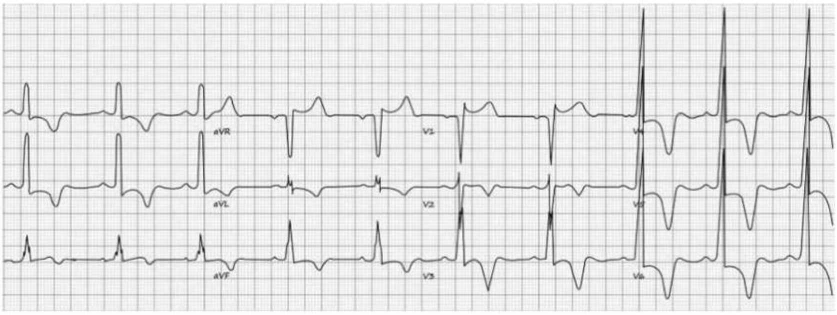
2.EEG



- Left Ventricular hypertrophy (Depth of S wave in V1 + Height of R in V5/V6 > 35mm)
- Deep T inversion
- G waves (inferior and lateral leads)
- Atrial Fibrillation

3.Holter

4.Cardiac MRI

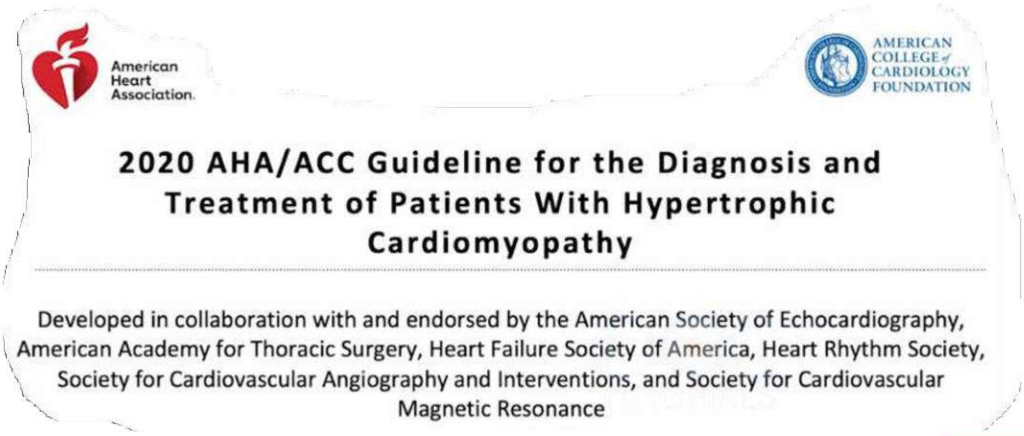
5.Cardiac catheterization:

- Brockenbrugh Braun Wald Morrow sign

↓

In HCM, paradoxical decrease in pulse pressure following a premature ventricular contraction (normally pulse pressure should increase)

Treatment 00:48:27



2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy

Developed in collaboration with and endorsed by the American Society of Echocardiography, American Academy for Thoracic Surgery, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society for Cardiovascular Magnetic Resonance

- If patient is symptomatic first choice of drug Is beta blockers → ↓ HR and ↓O2 consumption
- verapamil – calcium channel blocker
- Disopyramide → decrease LVOTO
- Medical management fails
  - Surgical myomectomy
  - Alcohol based septal ablation

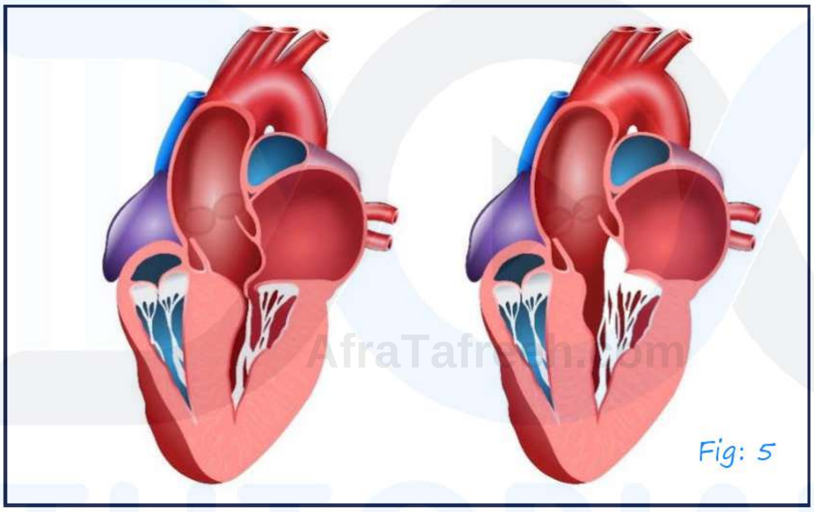


Fig: 5

- ICD → Indicated when there are risk factors for sudden cardiac death

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Risk factors for sudden death in hypertrophic cardiomyopathy		
Major risk factor		Screening technique
History of cardiac arrest or spontaneous sustained ventricular tachycardia		History
Syncope	Nonvagal often with or after exertion	History
Family history of sudden cardiac death		Family history
Spontaneous non sustained ventricular tachycardia	>3beats at rate >120	Exercise or 24-48h ambulatory recording
LV thickness >30mm	Present in <10% of patients	Echocardiography
Abnormal blood pressure response to exercise	Systolic blood pressure falls or failure to increase at peak exercise	Maximal upright exercise testing

RESTRICTIVE CARDIOMYOPATHY

Introduction 00:00:50

Restrictive Cardiomyopathy

- Myocardial disorder characterised by prominent diastolic dysfunction
- Diastolic dysfunction occurs in stiff non-compliant ventricles
- Diastolic dysfunction
- Ventricular wall thickness Normal
- Ventricular cavity dimensions Normal

Etiology 00:03:52

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- Amyloidosis – Most common is AL type
- Sarcoidosis
- Fabry's disease
- Glycogen storage disorders
- Hemochromatosis
- Associated with radiation
- Systemic sclerosis
- Endomyocardial fibrosis (RVE MF) → South India

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Clinical features 00:07:25

- Predominantly features of right sided failure
  - Pedal edema
  - Ascites

↓

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- Orthopnea] Left side failure
- PND

- There is a choice for thromboembolic events
- Increased incidence of atrial fibrillation

Examination findings 00:10:53

- Right sided failure – pedal edema
  - Ascites
  - Tender hepatomegaly
  - Increase JVP → Kussmaul sign⊕ (**paradoxical increase in jvp with inspiration)**
  - S_4 ⊕
  - Atrial fibrillation
- DD: Constrictive pericarditis

Investigations 00:13:50

i. TTE: IOC

- Diastolic dysfunction
- LV wall thickness] Normal
- LV cavity dimensions
- LV end diastolic pressure (LVEDP) increases

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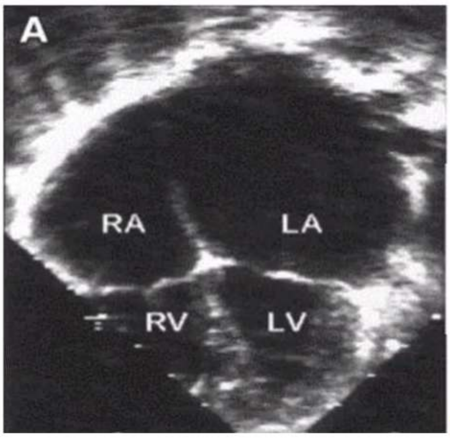

Fig: 1

Bilateral atria enlarged

Fig: 2

- In amyloidosis: Ventricular wall thickness increased

ii. Cardiac MRI

Fig: 3

Speckled glittering appearance

iii. ECG: Non specific

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- In amyloidosis → low voltage complexes

iv. CXR: cardiomegaly

v. Endomyocardial biopsy

Treatment 00:21:23

- Treatment of underlying cause
- Judicious use of loop diuretics
- Anticoagulant therapy

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ARRHYTMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Introduction 00:00:28

- Also, known as ARVD –arrhythmogenic right ventricular dysplasia
- Autosomal dominant
- Genetic mutation – either involving
  - Desmosomal junctional proteins (plakoglobin)
    (or)
  - Proteins interacting with desmosomes
- Impact of genetic mutation
  ↓
  - Myocardium gets replaced by fat & fibrous tissue
  - Both ventricles affected

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Clinical presentation 00:04:18

- Right sided heart failure
  - LV failure
  - Biventricular failure
- Arrhythmias – ventricular tachycardia
- Sudden death

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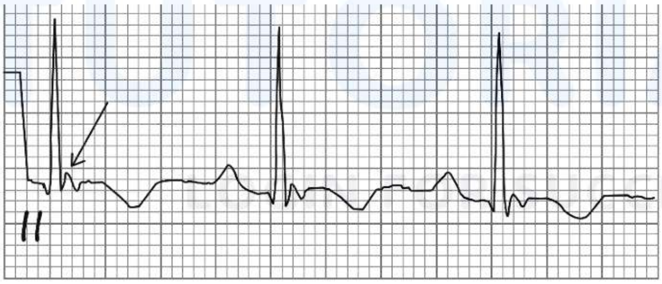
Naxos syndrome Fig: 1

- Naxos syndrome

↓

Woolly hair

Hyperkeratosis of palms and soles



ECG – Epsilon wave Fig: 2

- ECG – Epsilon wave

↓

Small depolarization after QRS is because of the excitation of surviving cardiomyocytes between fibrofatty tissue.

LEFT VENTRICULAR NON-COMPACTION (LVNC)

Introduction 00:00:22

- Characterised by normal myocardial maturation.
- As the heart develops, trabeculations disappear and heart becomes compact
  ↓
  arrest in this → LVNC
- Characterised by left ventricular endomyocardial trabeculations
- Tafazzin gene (TFZ) mutation (+)

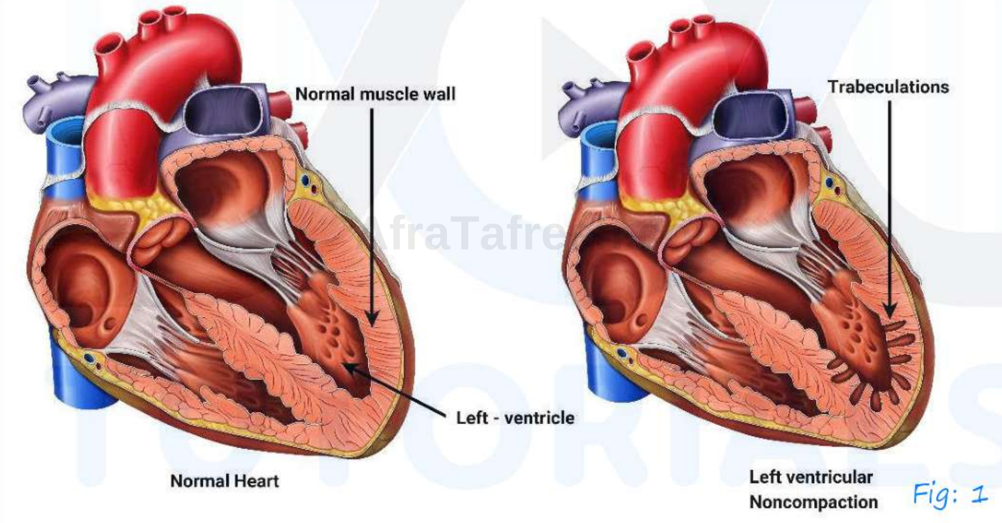


Fig: 1

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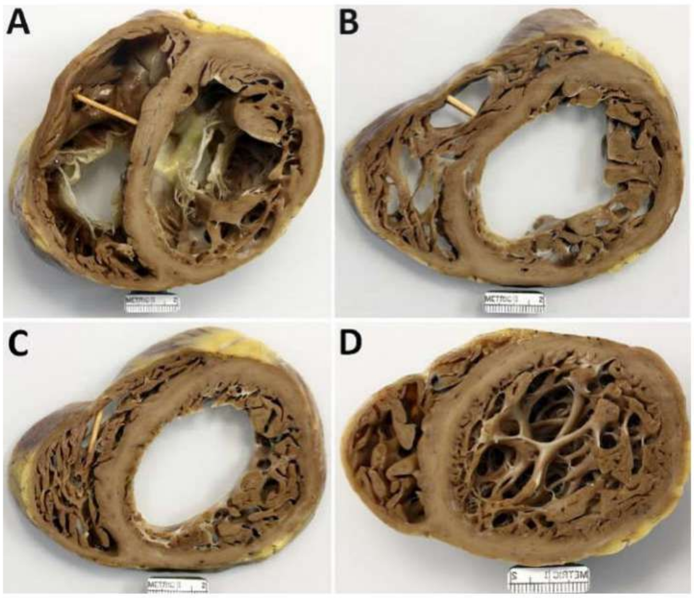

Fig: 2

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Clinical features 00:04:52

- Heart failure
- Arrhythmias
- Embolic events.

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TAKOTSUBO CARDIOMYOPATHY

Introduction 00:00:32

- Characterized by acute LV systolic failure
- Occurs in response to surge of catecholamines release → Occurs in response to intense physical/emotional stress
- Also referred to stress cardiomyopathy (or) Stress induced cardiomyopathy
- Predominant in past menopausal females (90%) (In Japan – Most common in males)

Pathogenesis 00:03:02

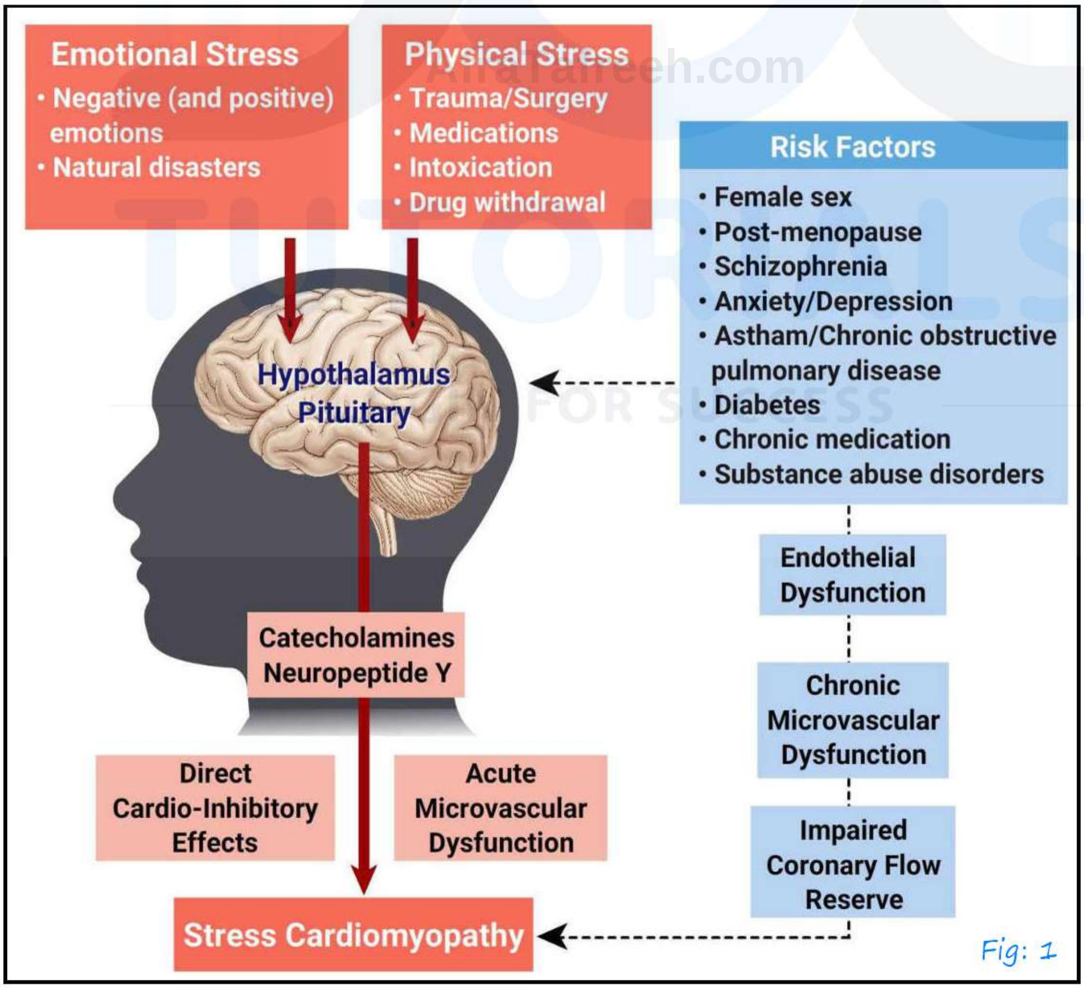

Fig: 1

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- Also known as broken heart syndrome
- Also, ref to as Apical ballooning syndrome

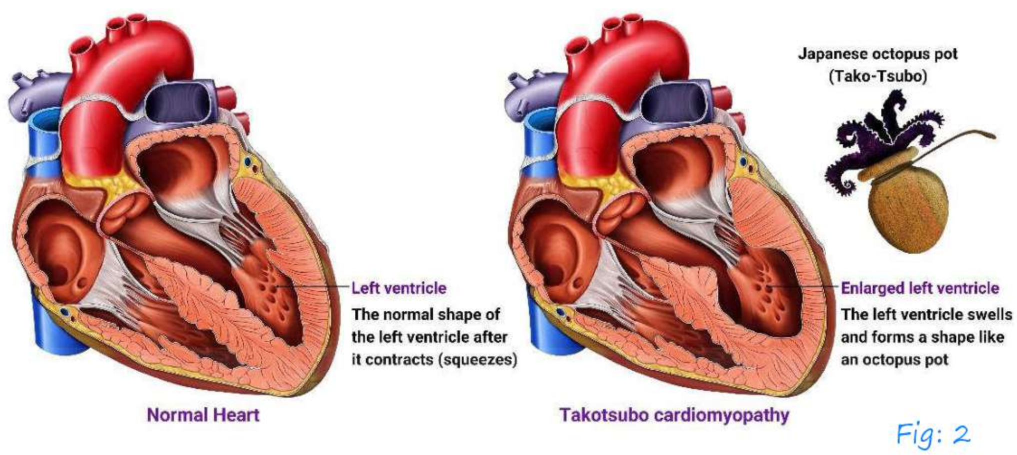

Fig: 2

- In Tonkotsu → Basal contraction + apical ballooning

Clinical presentation 00:08:28

- May be like acute myocardial infarction (or) acute pulmonary edema
- Cardiac biomarkers increase
- ECG changes → ST increases
  T inversion

Diagnostic criteria 00:09:57

- Revised mayo clinic Diagnostic criteria
  i. Transient hypokinesis, akinesis (or) dyskinesis of the left ventricular mid segments with (or) without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always, present
  ii. Absence of obstructive coronary artery disease (or) angiographic evidence of acute plaque rupture

iii. New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin

iv. Absence of pheochromocytoma (or) myocarditis

- In 21 Days, there is reversibility of acute systolic LV dysfunction
- Around 10% cases of takotsubo cardiomyopathy may have recurrence.

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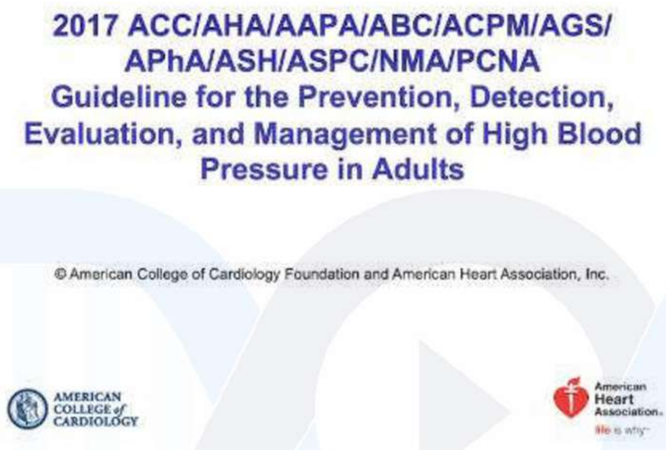
HYPERTENSION

Management of hypertension 00:00:15

- 2017 guidelines by American college of cardiology and American heart association



- 2018 – European society of cardiology and European society of HTN guidelines

DOC TUTORIALS
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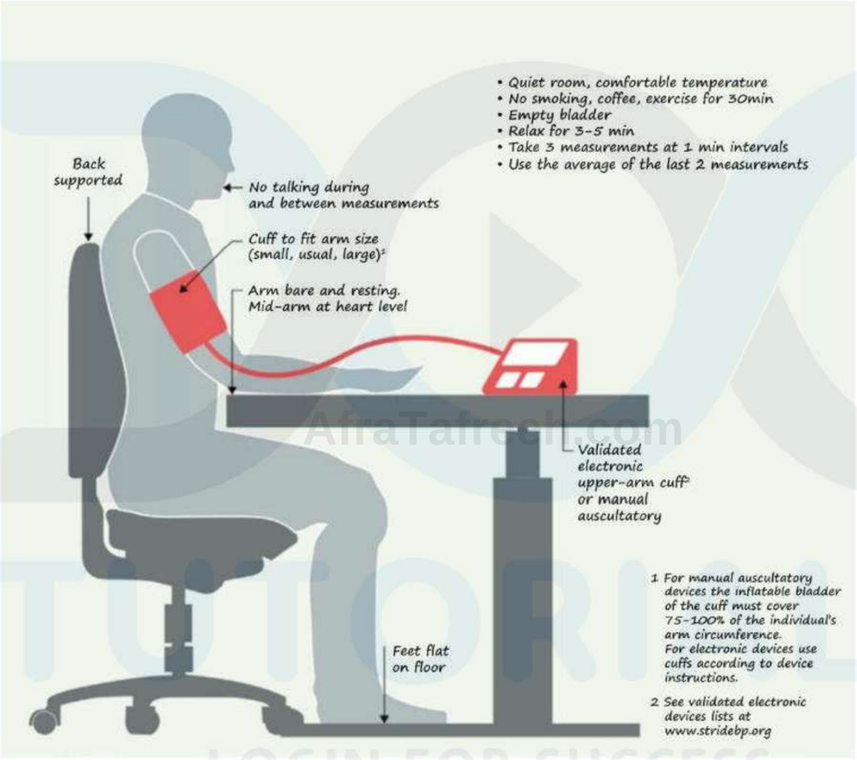
- 2020 international society of HTN guidelines



- Classification of HTN

Classification of hypertension based on Office blood pressure (BP) measurement			
Category	Systolic (mmHg)		Diastolic (mmHg)
Normal BP	<130	and	<85
High-normal BP	130-139	and/or	85-89
Grade 1 Hypertension	140-159	and/or	90-99
Grade 2 Hypertension	≥160	and/or	≥100

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- If individual has BP 126/88 mmHg

↓

High normal BP

142/120 mmHg → grade 2 HTN

- Ambulatory blood pressure monitoring (ABPM) 24 hours recording → average recording

Taken → Total daily

Morning

Night

Hypertension based on Office-, Ambulatory BPM) and Home Blood Pressure (HBPM) measurement		
		SBP/DBP (mmHg)
Office BP		≥ 140 and/or ≥90
ABPM	24h average	≥ 130 and/or ≥80
	Day Time (or awake) average	≥135 and/or ≥85
	Night Time (or asleep) average	≥ 120 and/or ≥70
HBPM		≥135 and/or ≥85

ISH vs ACC/AHA Guidelines			
International society of hypertension	Systolic (mmHg)		Diastolic (mmHg)
Normal BP	<130	and	<85
High-normal BP	130-139	and/or	85-89
Grade 1 Hypertension	140-159	and/or	90-99
Grade 2 Hypertension	≥160	and/or	≥100

	SBP		DBP
Normal	<120 mm Hg	an	<80 mm Hg
Elevated	120-129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130-139 mm Hg	or	80-89 mm Hg
Stage 2	≥140mm Hg	or	≥ 90 mm Hg

50-year-old male referred to you for anemia. BP was 144/96mmHg (first reading)- DO NOT DIAGNOSE AS HYPERTENSION BASED ON ONE VISIT

Blood Pressure Measurement and Diagnosis of Hypertension		
ESSENTIAL		
BP Measurement Plan according to Office BP levels		
Office blood pressure levels (mmHg)		
<130/85	130-159/85-99	>160/100
Remeasure within 3 years (1 year if other risk factors).	If possible, confirm with out-of-office measurement. - Alternatively, co repeated office visits.	Confirm within a few days/weeks.

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- 2-3 office visits in 1–4-week intervals

↓

High BP → then confirm as HTN

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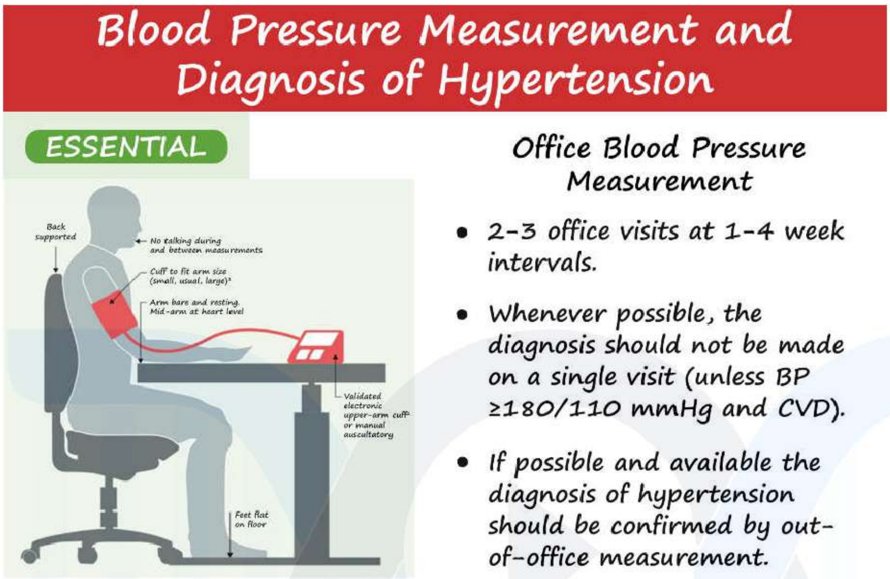
- If BP>180/110 mmHg and patient has some cardiovascular disease

  ↓

  Diagnose HTN in first visit



Isolated systolic HTN: - 00:35:00

- Systolic BP ≥ 140 mmHg
- Diastolic < 90 mmHg
- Seen in young adults/elderly

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Evaluation of patient with hypertension

- History
  - Symptoms
  - Other risk factors
  - Medication (NSAID's, combined OCP's tricyclic antidepressants , SNRI, erythropoietic stimulating agents)
  - Symptoms and signs of secondary HTN
- Examination

- Bruits
- Heart sounds/murmurs
- Basal crepitus
- Fundus → HTN retinopathy

- Lab investigations
  - Electrolytes (Na^+, K^+)
    - Creatinine
    - eGFR
    - KBS
    - Fasting lipid profile
    - Urine dipstick proteinuria
    - ECG: – atrial fibrillation ,Lt ventricular hypertrophy ischemic heart disease

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Diagnostic and Clinical Tests
ESSENTIAL
Medical History (BP, risk factors, co-morbidities, signs/symptoms of secondary hypertension...)
Physical Examination (circulation, heart, other systems)
Lab Investigations (Na+, K+, creatinine, eGFR, dipstick lipids, Fasting Glucose where available)
12 lead ECG (AF, LV hypertrophy, IHD...)
OPTIMAL
Additional tests to consider (extended biochemistry, cardiac/kidney/brain/vascular imaging, fundoscopy...)

- in ideal setting

  1.carotid doppler → measure intima media thickness, plaques

  2.ABPI

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3.ECHO

- HMOD → Hypertension mediated organ damage

Hypertension-mediated Organ Damage	
HMOD Assessment	
ESSENTIAL	OPTIMAL
Serum creatinine	Brain
eGFR	Eyes
Dipstick urine test	Heart
12-lead ECG	Kidneys
	Arteries
Serial assessment of HMOD	
may help to determine efficacy of treatment	

- Brain – CT Brain
- Heart – echo
- Kidneys – Renal artery doppler
- Eyes – fundoscopy

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Management 00:48:13

Life systyle modification

- Salt restricted diet
- DASH diet
  - Dietary approaches to stop HTN

- Rich in whole grains, fruits, vegetables, low fat dairy products, less of saturated and trans fats

- Rich in K^+, Mg^{2+}, Ca^{2+} diet
- Increased nitrates → green leafy vegetables beet root
- Quit smoking
- Reduce alcohol
- Exercise → 30 minutes/day 5-7 days/week
- Weight reduction
- Stress reduction
- Reduce air pollution

Pharmacological methods

i. When to start medication?

- Systolic BP: - 140-159 mmHg

  And/or

  Diastolic BP: - 90-99 mmHg

  - Low risk group

    ↓

    Lifestyle modification and follow up

  - High risk
    - (HMOD)
    - CKD
    - DM
    - CVD

    ↓

    Initiate drug therapy

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- Syst BP >160 mmHg

  And/or

- Diastolic BP>100 mmHg

} Initiate drug therapy

ii. What medication?

- Step 1: - combination therapy

  (A + C) → single pill + low dose

  ACEI/ARB'S

  DHP CCB – Amlodipine

  Monotherapy → very old > 80 years

  Low risk HTN

Telmisartan 40mg + Amlodipine 5 mg → single tablet

↓

Either morning or night

Therefore, Target BP: -

- <65 years: - <130/80 mmHg
- ≥ 65 years: - <140/90 mmHg

Drug Treatment of Hypertension
Summary 1
In established hypertension, uncontrolled by lifestyle measures:
Drug Treatment Threshold
≥140/90 mmHg (raising to ≥160/100 mmHg for those at lowest risk)
Drug Treatment Target
OPTIMAL <65 years: <130/80 mmHg ESSENTIAL ≥65 years: <140/90 mmHg reduce BP by >20/10 mmHg

If target is not achieved in 3 months,

- Step 2: - A + C – High dose

  Telmisartan 80mg + Amlodipine 10 mg

  ↓↓

- Step 3: - A + C + D

  Diuretics → thiazide /thiazide like chlorthalidone and

  Hyprochlorthalidone

  ↓↓

  Not controlled

  - Resistant HTN → BP not controlled with 3 antihypertensives at maximum tolerance dose one of which is a diuretic

- Step 4: - A + C + D + spironolactone

  Clonidine

  Beta blockers

  - Spironolactone is not given if eGFR <45ml/min (or) K^+ > 4.5 meq/L
  - Post stroke/cardiac dysfunction → step 1 → A + D

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Management of hypertension associated with comorbidities 01:11:00

Co-morbidities	When to start	Target	First line	LDL Target
Coronary Artery Disease	≥140/90 mm Hg	<130/ 80 mHg <140/ 80 mmHg (in elderly)	RAS blockers, Beta blockers CCBs can also be considered	<55 mg%
Previous stroke (Ischemic/Hemorrhagic)	≥140/90 mm Hg	<130/80 mHg <140/80 mHg (in elderly)	RAS blockers, CCBS, Diuretics	<70 mg%
CKD	≥140/90 mm Hg	<130/80 mHg <140/80 mHg (in elderly)	RAS blockers CCBs and Diuretics can be added	
Heart Failure	≥140/90 mm Hg	<130/80 mHg But >120/70 mmHg	RAS blockers, Beta blockers, Aldosterone antagonists	
diabetes	≥140/90 mm Hg	<130/80 mHg <140/80 mHg (in elderly)	RAS blocker	

↓

Management of HTN associated with commonalities ISH 2020 guidelines

Anti-Hypertensive Drugs 01:20:20

Drug	Contraindications	
	Compelling	Possible
Diuretics (thiazides/thiazide type, e.g. chlorthalidone and indapamide)	Gout	Metabolic syndrome Glucose intolerance Pregnancy Hypercalcemia Hypokalemia
Beta-blockers	Asthma Any high-grade sino-atrial or atrioventricular block Bradycardia (heart rate <60 beats per min)	Metabolic syndrome Glucose intolerance Athletes and physically active patients
Calcium antagonists (dihydropyridines)		Tachyarrhythmia Heart failure (HFrEF, class III or IV) Pre-existing severe leg oedema
Calcium antagonists (verapamil, diltiazem)	Any high-grade sino-atrial or AV block Severe LV dysfunction (LV EF < 40%) Bradycardia (heart rate < 60 beats per min)	Constipation
ACE inhibitors	Pregnancy Previous angioneurotic oedema Hyperkalemia (potassium > 5.5 mmol/L) Bilateral renal artery stenosis	Women of child-bearing potential without reliable contraception
ARBs	Pregnancy Hyperkalemia (potassium > 5.5 mmol/L) Bilateral renal artery stenosis	Women of child-bearing potential without reliable contraception

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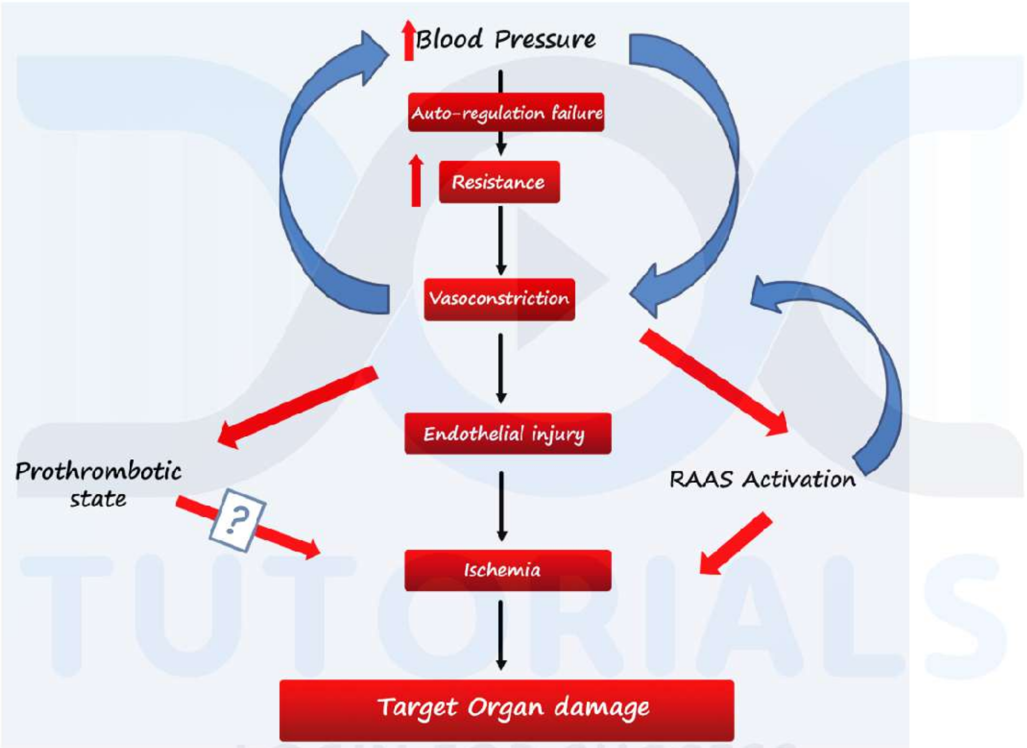
Hypertensive emergency	Hypertensive urgency
ISH 2020 guidelines - BP >200/120 mmHg	Hypertensive crisis
ACC-AHA guidelines – BP> 180/120 mmHg	Hypertensive crisis
Hypertensive emergency • HTN crisis + HMOD • Requires aggressive therapy • IV antihypertensives	Hypertensive urgency • HTN crisis, No HMOD • Oral antihypertensives to follow up



Hypertensive crisis

Always rule out secondary HTN

HTN

Primary 1°	2° (Secondary)
Essential	Resistant HTN
Polygenetic	Young onset HTN (<30 years)
Mechanism	HTN crisis

Causes of 2° HTN

Causes of Secondary Hypertension with Clinical Indications
Common causes
Renal parenchymal disease
Renovascular disease
Primary aldosteronism
Obstructive sleep apnea
Drug or alcohol induced
Uncommon causes
Pheochromocytoma/paraganglioma
Cushing's syndrome
Hypothyroidism
Hyperthyroidism
Aortic coarctation (undiagnosed or repaired
Primary hyperparathyroidism
Congenital adrenal hyperplasia
Mineralocorticoid excess syndromes other than primary aldosteronism
Acromegaly

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- Drugs
  - NSAIDS
  - Cyclosporine
  - Tacrolimus
  - OCPLS

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Management of HTN emergencies 01:38:01

	Clinical presentation	Timeline and target DP	1st line treatment	Alternative
Hypertensive Emergencies	Malignant hypertension with or without TMA or acute renal failure	Several hours MAP-20% to-25%	Labetalol Nicardipine	Nitroprusside Urapidil
	Hypertensive encephalopathy	immediate, MAP-20% to-25%	Labetalol Nicardipine	Nitroprusside
	Acute ischemic stroke and BP->220mmhg systolic or >120mmhg diastolic	1h, MAP-15%	Labetalol Nicardipine	Nitroprusside
	Acute ischemic stroke with Indication for thrombolytic therapy and BP>185mmhg systolic or >110 mmHg diastolic	1h, MAP-15%	Labetalol Nicardipine	Nitroprusside
	Acute hemorrhagic stroke and systolic BP > 180 mmHg	Immediate, Systolic BP 130<BP<180 mmHg	Labetalol Nicardipine	Urapidil
	Acute coronary event	Immediate, Systolic BP <140 mmHg	Nitroglycerine Labetalol	Urapidil

	Acute cardiogenic pulmonary	Immediate, Systolic BP <140 mmHg	Nitroprusside or nitroglycerine (with loop diuretic)	Urapidil (with loop diuretic)
	Acute aortic disease	Immediate, Systolic BP <120 mmHg and rate <60 BPM.	Esmolol and Nitroprusside or nicardipine	Labetalol or metoprolol
	Eclampsia and severe pre eclampsia/HELP	Immediate, Systolic BP <160 mmHg and diastolic BP <105 mmHg	Labetalol or nicardipine and Magnesium sulphate	

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ATHEROSCLEROSIS

Introduction 00:00:42

Atherosclerosis

- Chronic vascular inflammation predominantly affects medium and large sized arteries
- Vessels involved:
  - Coronary arteries
  - Cerebral blood vessels
  - Aorta
  - Peripheral arteries
  - Renal arteries

Pathogenesis 00:04:34

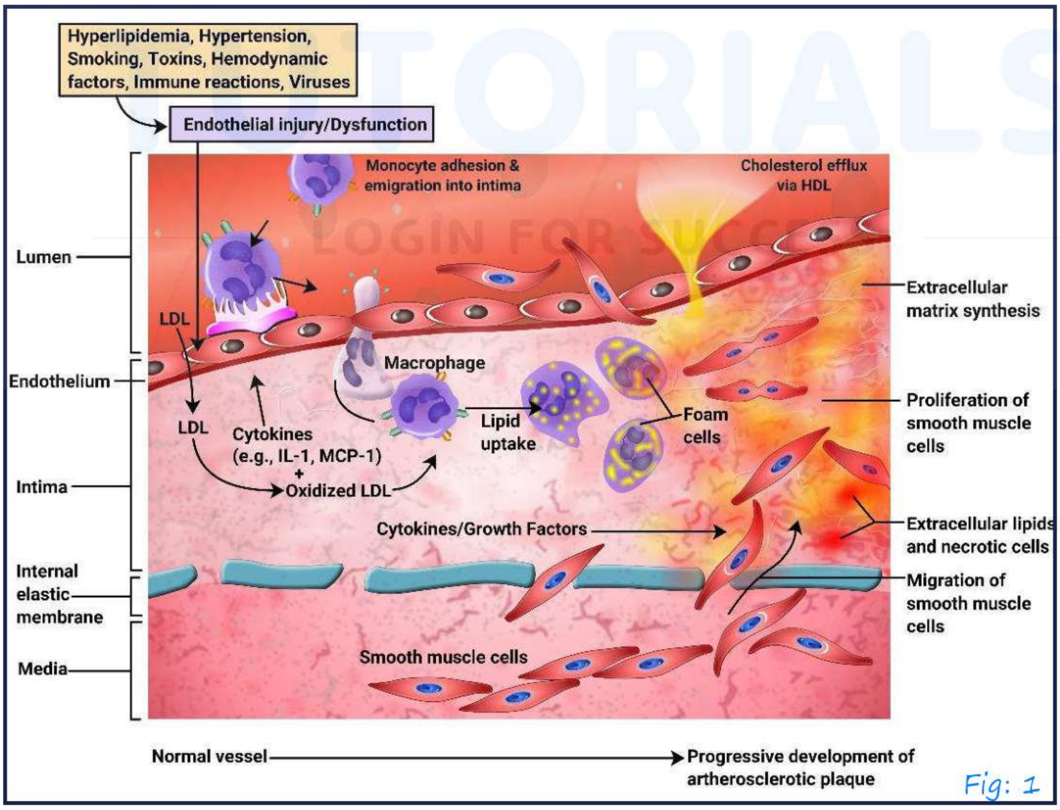

Fig: 1

- Blood vessel wall has trilaminar structure
  - T. intima
  - T. media
  - T. adventitia
- Layer found between T. intima and T. media is internal elastic lamina
- Initiating event → endothelial injury

↓

Can be a sequalae of hyperlipidemia

Hypertension

Toxins

Smoking

Immune mediated

Endothelial injury

↓

Recruitment of inflammatory cells

↓

Release of Adhesion molecules

↓

Monocytes gain access through endothelium to the vessel wall (T. intima)

↓

In tunica intima – scanty smooth muscle cells extracellular matrix

↓

Release of growth factors

↓

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Recruitment of smooth muscle cells from T. media to T. intima

↓

In T. intima → proliferation of smooth muscle cells as well as extracellular matrix

↓

- Increase in T. intima thickness
- LDL → oxidized LDL

↓

Taken up by macrophages (Foamy macrophages / foam cells)

↓

Atherosclerotic plaque in tunica intima

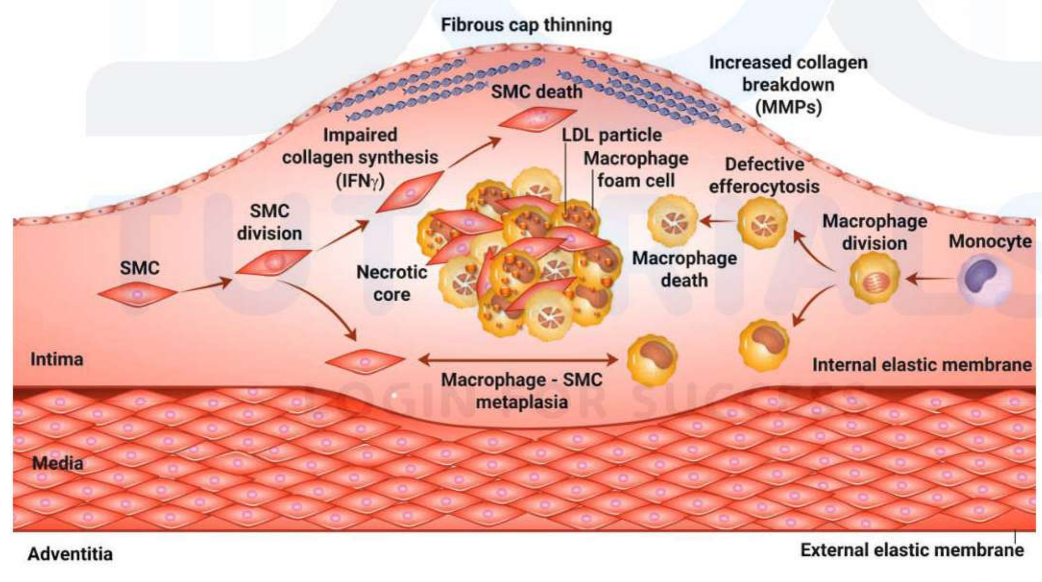

Fig: 2

Types of plaques

- Stable plaques: - less likely to rupture thick fibrous cap plenty of smooth muscle cells and extracellular matrix

- Vulnerable plaque: - more likely to rupture thin fibrous cap plenty of inflammatory cells
- Unstable plaque: - that has ruptured
- Thin fibrous cap because of matric metalloproteases may cause dissolution
- Plaque ruptures

  ↓

  Platelets interact with subendothelial collagen

  ↓

  Thrombus

  ↓

  Infraction.

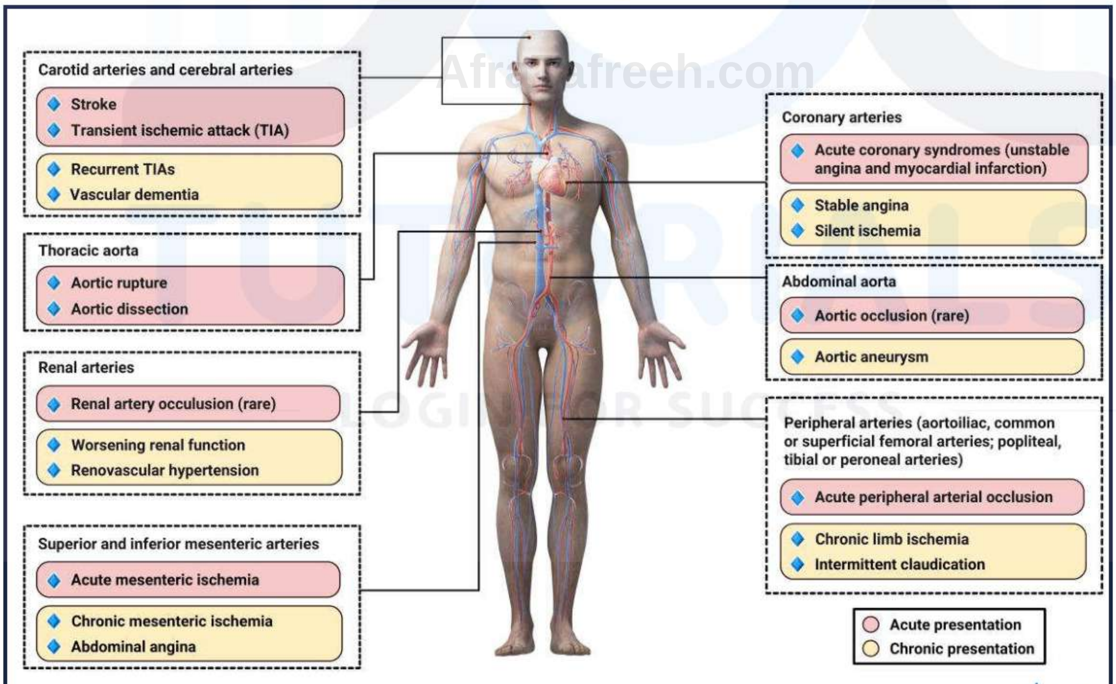

Fig: 3

Imaging 00:24:49

1.Carotid ultrasound:

Vessels are prone to atherosclerosis at

- Bifurcations

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- Areas of Low shear stress

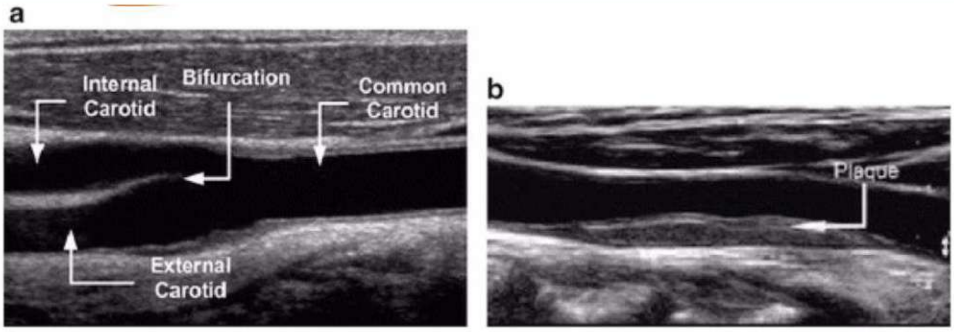

Fig: 4

2.IVUS – Intravascular ultrasound

- Invasive procedure
- Able to visualize histology of atherosclerotic plaque

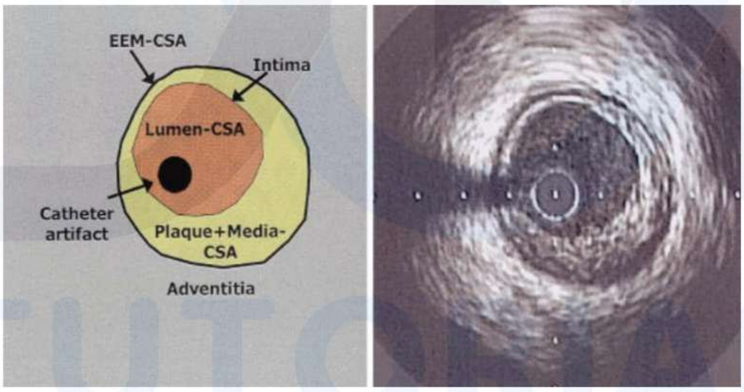

Fig: 5

3.Optical coherence tomography (OCT)

- High-resolution cross-sectional images of coronary arteries

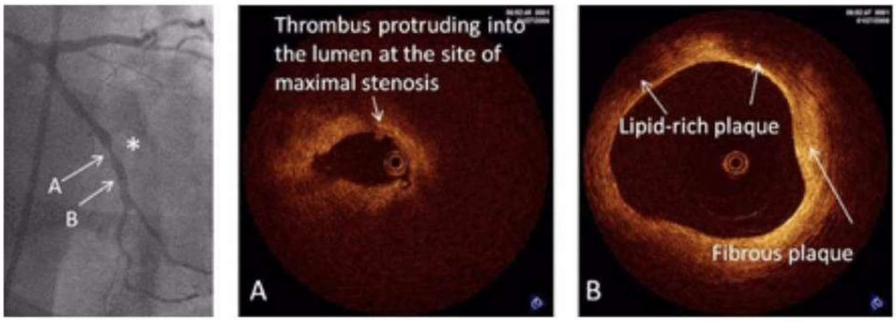

Fig: 6

4.Coronary CT calcium score

- Larger the atheroma, more will be the calcium burden
- AGATSON score is used
- Used as a surrogate marker of atherosclerosis

5.CT angio

6.MR angio

7.Catheter based angio

8.FDG PET.

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CHRONIC STABLE ANGINA

Introduction 00:00:26

- IHD: ISCHEMIC HEART DISEASE
  - Heterogenous group of disorders
  - Mismatch between myocardial O_2 supply and demand

Stable IHD (Chronic stable angina) → ACS (Acute Coronary Syndromes)

↓

Unstable angina

NSTEMI

STEMI

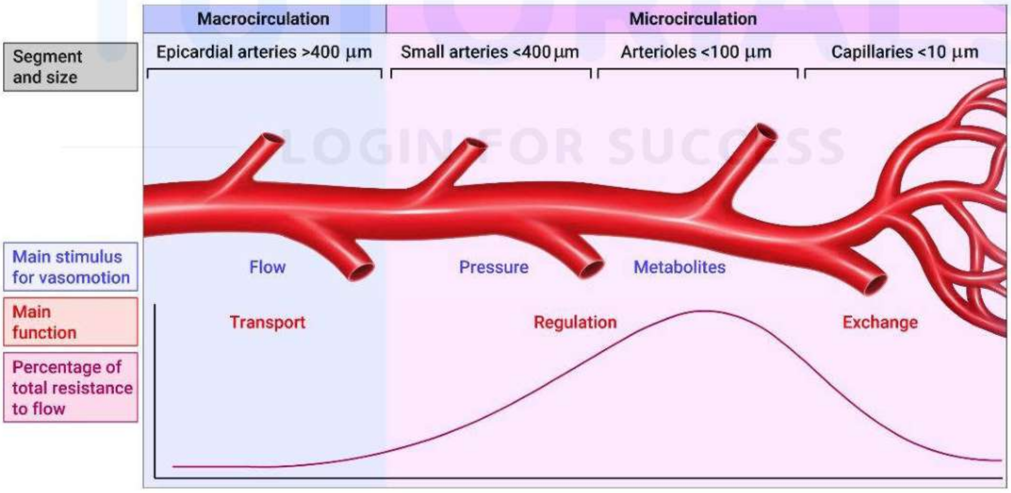


Fig: 1

- Myocardium is supplied by coronary arteries

i. Microcirculation → Contributed by epicardial coronary artery

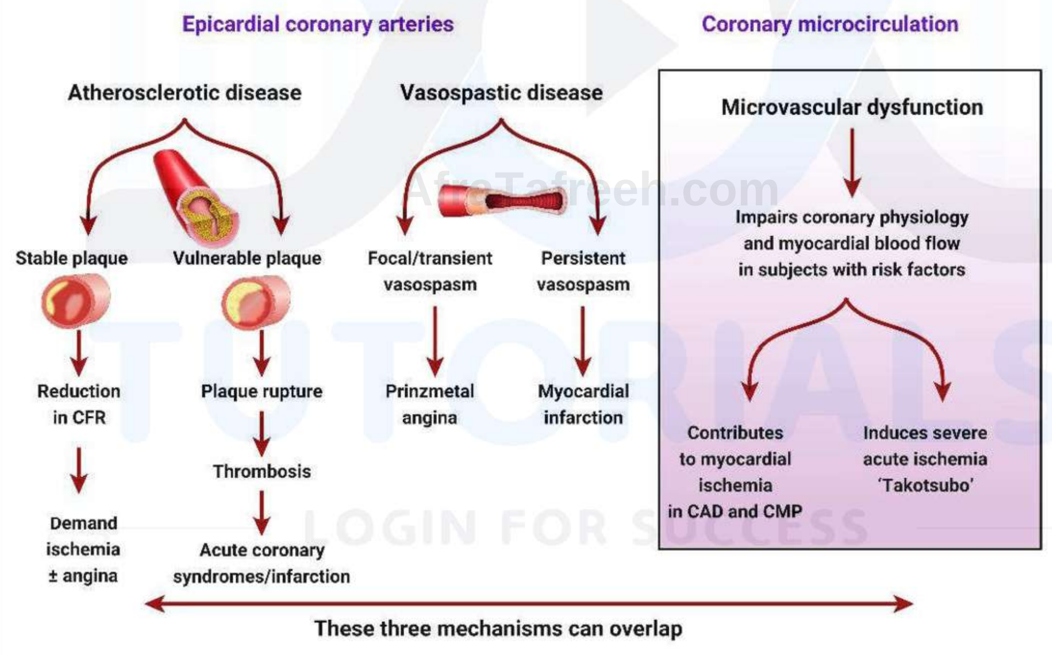
ii. Microcirculation →

-Small arteries

- Arterioles

- Capillaries

- Maximum resistance to flow → Arterioles
- Blood supply increases when demand increases
- Epicardial coronary artery may predispose to atherosclerosis



Mechanisms of myocardial ischemia Fig: 2

- CFR – Coronary flow reserve

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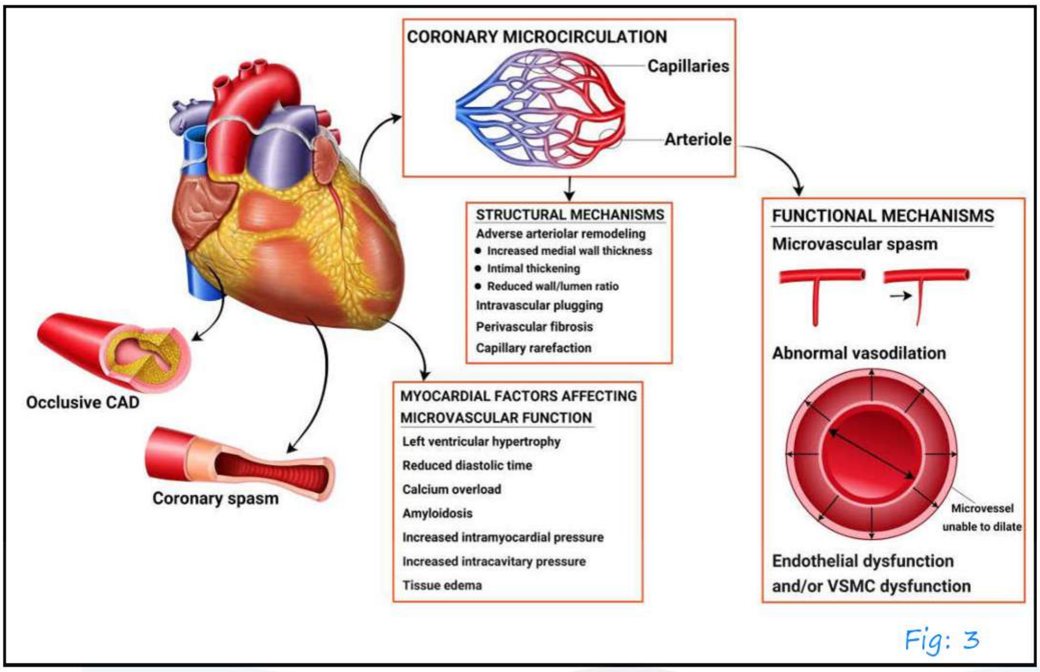

Fig: 3

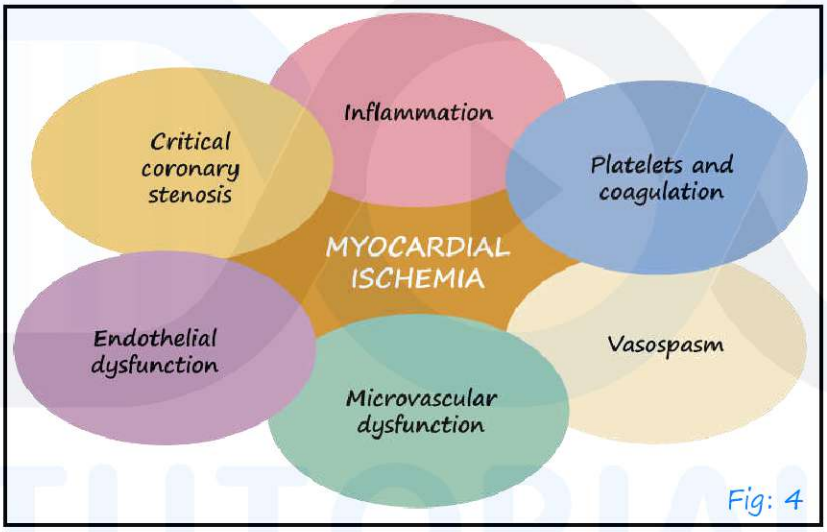

Fig: 4

Chronic stable angina 00:19:50

- Male > Female

Risk factor 00:21:18

- Risk factors → Age
  Obesity
  Sedentary life style
  DM
  Systemic HTN
  Dyslipidemia

Pathophysiology 00:22:25

- Pathophysiology of CSA
  - Reversible ischemia

Clinical features 00:23:10

- Clinical features – Anginal episodes
  ↓
  - Substernal pain — Clenched fist ↓ levine's sign
    - Heaviness
    - squeezing
    - pressure
  - Lasts for 5-10 minutes
  - Crescendo – decrescendo type of pain
  - Pain may radiate
    - Left arm medial aspect (most common)
    - Right arm
    - Neck
    - Jaw
    - Interscapular region
    - Epigastrium
  - Worsened by exercise or emotion
    meals (post prandial angina)
    cold
    sexual intercourse
  - Relieved by rest or nitrates

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Investigations 00:30:37

1.ECG

- During anginal pain – ST depression
- No angina – Normal ECG

2.Cardiac biomarkers

- Trop I/T= normal (no myocardial injury)
- hs-CRP-Elevated

Investigations

1.TMT (Tread mill test) [Based on modified bruce protocol]

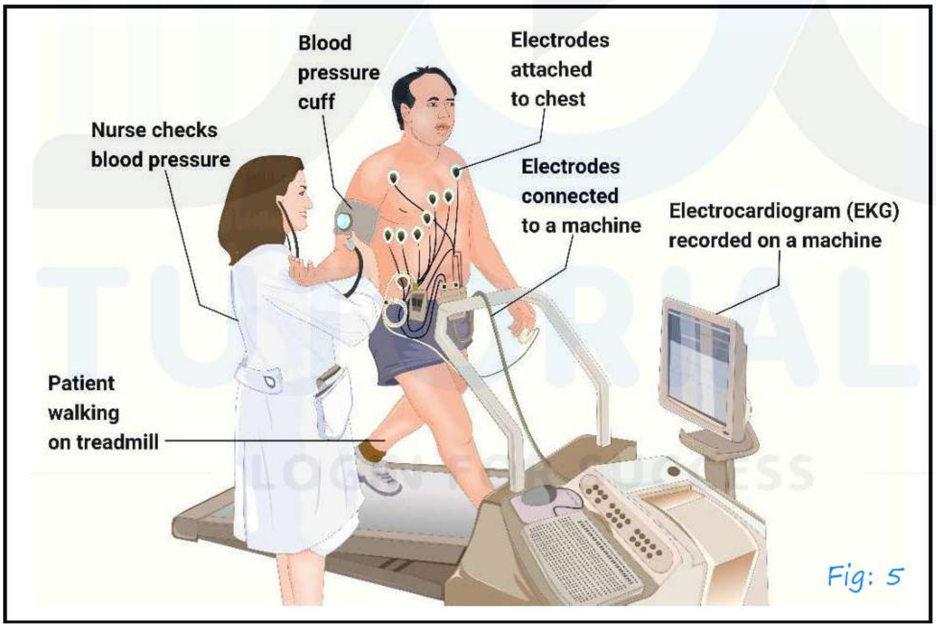

Fig: 5

- Every 3 min – speed increases

  ↓

  Progressively increase exercise workload
- Maximum possible HR →(220 – Age)
- Target HR – 85% maximum possible HR

Fig: 6

- ST depression ≥ 1 mm ≥ 80 m sec in 2 continuous leads

  ↓

  Ischemia changes

Absolute contraindications	Relative contraindications
- Active endocarditis - Acute aortic dissection - Acute myocarditis/pericarditis - Decompensated heart failure - Inability to exercise - Myocardial infarction in previous two days - Ongoing unstable angina - Symptomatic severe aortic stenosis - Uncontrolled cardiac arrhythmia with hemodynamic compromise	- Acquired complete heart block (left bundle branch block) - Hypertrophic obstructive cardiomyopathy with severe resting gradient - Known left main coronary artery disease - Recent stroke or transient ischemic attack - Resting systolic blood pressure >200 mmHg or diastolic blood pressure > 110 mmHG - Tachyarrhythmia with uncontrolled ventricular rate.

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Dukes score

Score	Risk	6-year survival %
> 5	Low risk	97
– 10 to +4	Moderate risk	91
< – 11	High risk	72

- No minutes on treadmill – (5 x ST depression in mm)

  – (4 x angina index)

- Low risk – Optical medical management
- Moderate risk ⎤ – Revascularization procedure
- High risk ⎦ PCI CABG

ECG Changes

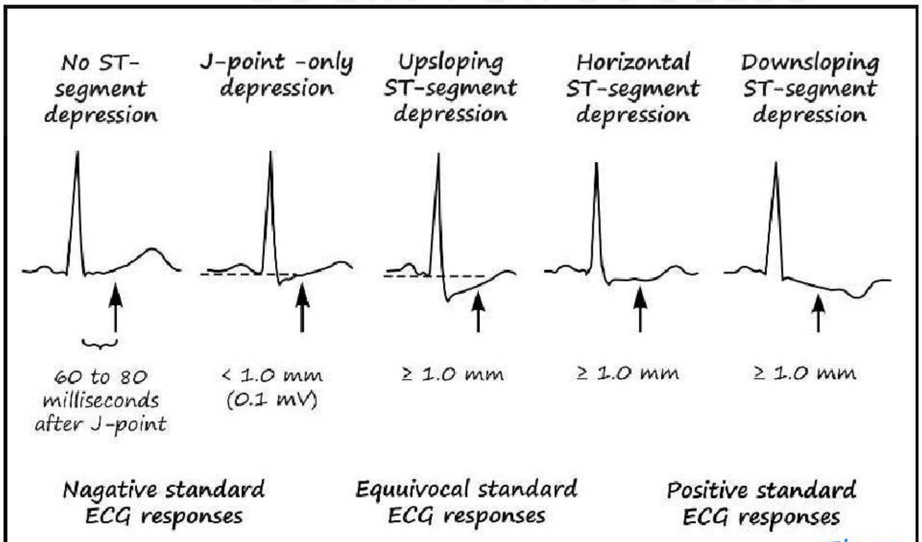

Fig: 7

2.Morbidly obese individual

↓

Pharmacological stress (dobutamine stress echo test)

↓

Dobutamine → acts on β_1 receptors

↓

Echo → baseline of dobutamine

Low
high
rest
] Regional hypokinesia/akinesia

3.Radionuclide perfusion studies

- Thallium 201
- Tc 99 sestamibi scan

4.PET scan

5.Gold standard – Coronary angiography (Invasive)

↓

Recurrent anginal episodes despite OMT

↓

Revascularization – PCI/CABG

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Management 01:02:29

- Goals of treatment – control of symptoms
  Prevent development of adverse cardiac outcomes.
- How?
  - Risk factors management
  - Anti anginal drug therapy
  - Revascularization

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Risk factor management

- Healthy diet → rich in fruits, vegetables, limit saturated & trans fats
- Cut down smoking & alcoholisms
- Manage DM

  HTN – sys < 140 mmHg
- Dyslipidemia – Moderate high intensity statin

  40-80 mg Atorvastatin

  20-40 mg Rosuvastatin
- Obesity – control weight
- 30 min daily exercise (based on patient)

Anti-anginal drug therapy

- β blockers – cornerstone

  → Decreases demand – supply mismatch

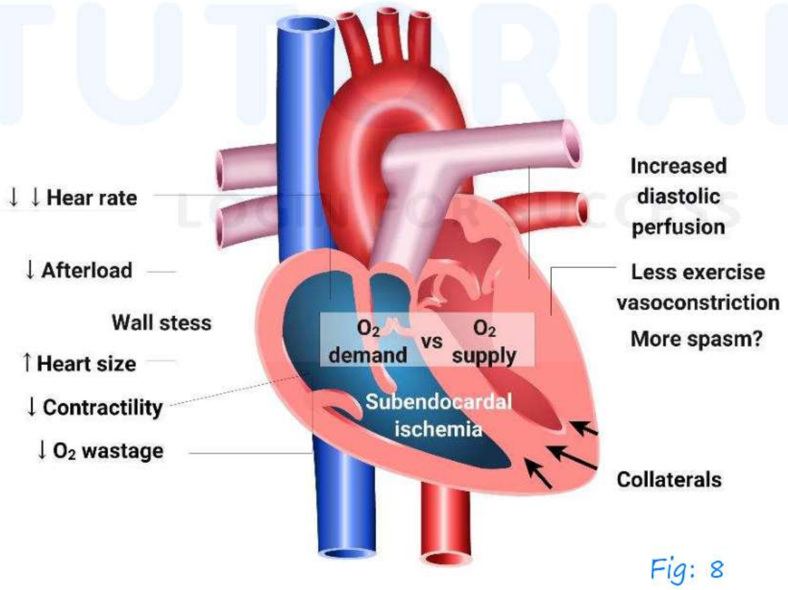

Fig: 8

- Metoprolol
- Carvedilol
- Nebivolol

Ideal Candidates	Poor Candidates
- Prominent relationship of physical activity to attacks of angina - Coexistent hypertension - History of supraventricular or ventricular arrhythmias - Previous myocardial infarction - LV systolic dysfunction - Mild to moderate heart failure symptoms (NYHA Functional Class II and III) - Prominent anxiety state	- Asthma or reversible airway component in patients with chronic lung disease - Severe LV dysfunction with severe heart failure symptoms (NYHA Functional Class IV) - History of severe depression - Raynaud phenomenon - Symptomatic peripheral artery disease - Severe bradycardia or heart block - Diabetes with frequent hypoglycemia episodes.

- Anti platelets
  - Aspirin 75 mg (Enteric coated preparation)
    ↓
    Intolerance
    ↓
    Clopidogrel
  - Routine dual antiplatelets
    ↓
    Previous MI within last 3 years

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- Nitrates
  - Increases NO → Increases cGMP
    ↓
    venodilatation
    ↓
    Decreases left ventricular end diastolic volume & pressure
  - Acts by coronary vasodilation
  - Antithrombotic

Nitrate Therapy in Patients with Ischemic Heart Disease		
Preparation of agent	Dose	Schedule
Nitroglycerin		
Ointment	0.5 – 2 in.	Two or three times daily
Transdermal patch	0.2 – 0.8 mg/h	Every 24h; remove at bedtime for 12-14h
Sublingual tablet	0.3 – 0.6 mg	As needed, up to three doses 5 min apart
Spray	One or two sprays	As needed, up to three doses 5 min apart
Isosorbide dinitrate		
Oral	10-40 mg	Two or three times daily
Oral sustained release	80-120 mg	Once or twice daily (eccentric schedules)
Isosorbide 5-mononitrate Oral	20 mg	Twice daily (given 7-8 h apart)
Oral sustained release	30-240 mg	Once daily

- Atleast there should be 8-hour nitrate free interval

  ↓

  If not, patient develops nitrate tolerance

- Calcium channel blockers

  Non DHP – verapamil

  Diltiazem

  DHP – Amlodipine

- Metabolic modulatory – Trimetazidine

  ↓ Ranolazine

  PFOX inhibitor (partial fatty acid oxidation inhibitors)

- Normally, heart uses fatty acids as fuel
- Metabolic inhibitors convert fatty acids to glucose

  ↓

  More efficient fuel

- Do not have ionotropic/chronotropic effect
- Ranolazine – affect the late sodium channels

Nicorandil

- Activated ATP sensitive K^+ channels
- NO release

Ivabradine

- Acts on funny sodium currents

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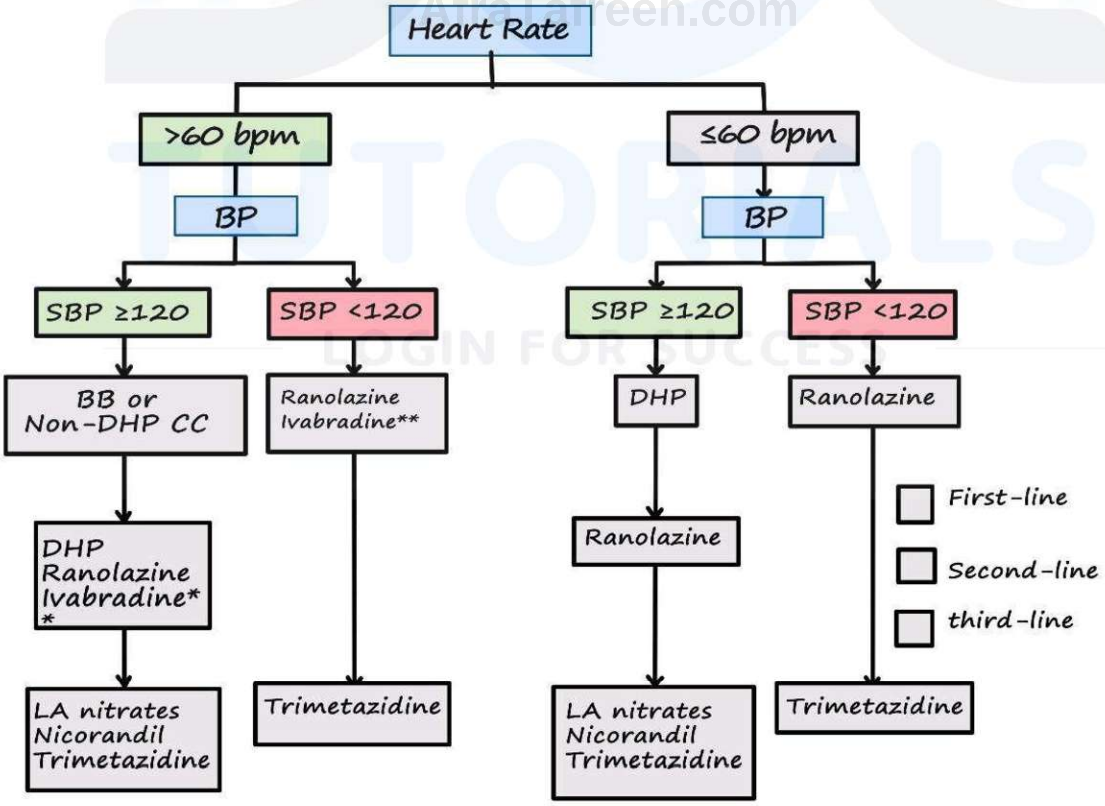
Anti Anginal Agents			
Agent	**Common side effects**	**Contraindications**	**Potential drug interactions**
Agents that have a physiological effect			
Short acting and long acting nitrates	Headache, flushing, hypotension, syncope and postural hypotension, reflex tachycardia	Hypertrophic obstructive cardiomyopathy	Phosphodiesterase type 5 inhibitors (sildenafil and similar agents), beta adrenergic blockers, calcium-channel blockers
Beta blockers	Fatigue, depression, bradycardia, heart block, bronchospasm, peripheral vasoconstriction, postural hypotension, impotence, masked signs of hypoglycemia	Low heart or heart conduction disorder, cardiogenic shock, asthma, severe peripheral vascular disease, decompensated heart failure, vasospastic angina; use with caution in patients with COPD (Cardio-selective beta blockers may be used if patient receives adequate treatment with long-acting beta agonists)	Heart rate lowering calcium channel blockers, sinus node or AV conduction depressors
Calcium channel blockers heart rate lowering agents	Bradycardia, heart conduction defect, low ejection fraction, constipation, gingival hyperplasia	Cardiogenic shock, severe aortic stenosis, obstructive cardiomyopathy	CYP3A4 substrates (digoxin, simvastatin, cyclosporine)

Dihydropyridine	Headache, ankle swelling fatigue, flushing, reflex tachycardia	Low heart rate or heart rhythm disorder, sick sinus syndrome, congestive heart failure, low blood pressure	Agents with cardiodepressant effects (beta-blockers, flecainide), CYP3A4 substrates
Agents that affect myocardial metabolism			
Ranolazine, Trimetazidine	Dizziness, constipation, nausea, QT – interval prolongation	Liver cirrhosis	CYP3A4 substrates (digoxin, simvastatin, cyclosporine), drugs that prolong the corrected QT interval



- Patients with angina and/or dyspnoea and coronary artery disease – Event prevention (12)

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Recommendation	Class	Level
Lipid-lowering drugs		
Statins are recommended in all patients with CSS.	I	A
If a patient's goal is not achieved with the maximum tolerated dose of stain, combination with ezetimibe is recommended.	I	B
For patients at very high risk who do achieve their goal on a maximum tolerated dose of stain and ezetimibe, a combination with a PCSK 9 inhibitor is recommended.	I	A
Ace Inhibitors		
ACE Inhibitors (or ARBs) are recommended if a patient has other conditions (e.g. heart failure, hypertension, or diabetes).	I	A
ACE inhibitors should be considered in CCS patients at very high risk of cardiovascular events.	IIa	A

- What if patient is not controlled with medication

↓

Revascularization therapy

↓

- Drug refractory angina
- Optimum medical management

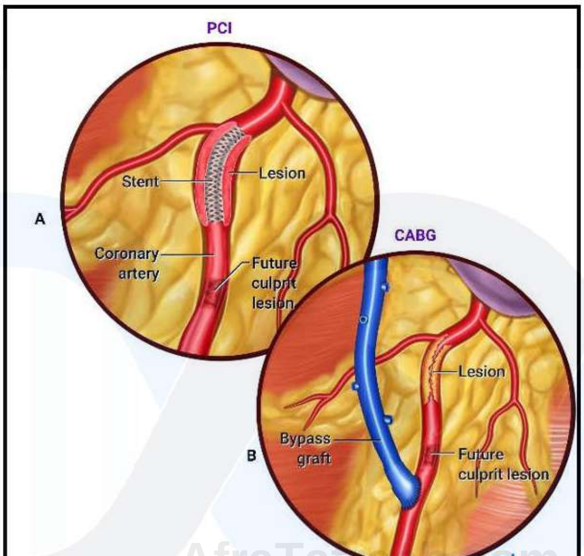

Fig: 9

Percutaneous coronary intervention

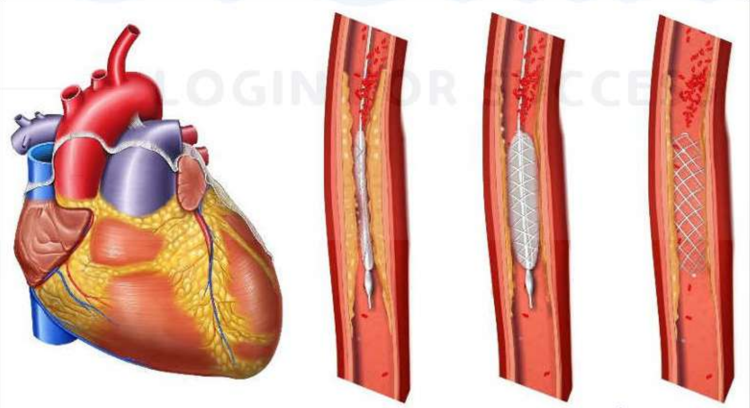

Fig: 10

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1.Gain access through radial or femoral route

↓

Seldinger's technique

↓

Guide wire reaches coronaries

↓

Balloon dilation

↓

Stent in situ

- Stents – 20% chance of restenosis within 6 months

With bare metal stents

↓

Drug eluting stents used

→ Everolimus] anti-proliferative drugs
Sirolimus]

– <10% restenosis in 6 months

- Before procedure → loading dose of dual antiplatelets

↓

300 mg aspirin

600mg clopidogrel

- During procedure – UFH

or

I.V Gp IIb/IIIa inhibitors

↓

– Abciximab

– Eptifebatide

- Tirofiban

- Post procedure → Dual antiplatelets for 1 year

  ↓

  max. chance for stent thrombosis

Coronary artery bypass grafting

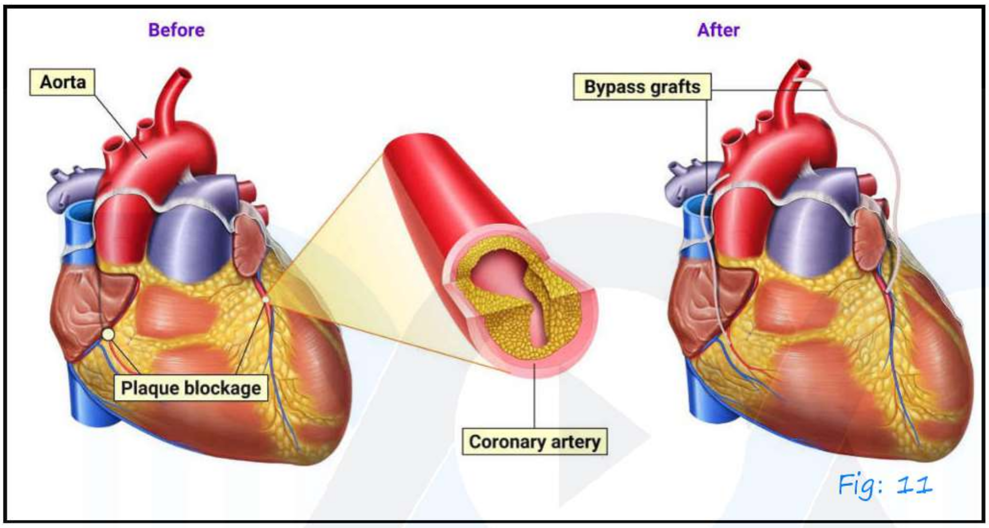

Fig: 11

- Bypass between aorta and coronaries distal to region of blockade
- Arterial graft – Internal mammary artery
  Radial artery
- Venous graft – Great saphenous vein

PCI vs CABG

- Single vessel disease ⎤ PCI favored
- Double vessel disease ⎦
- Triple vessel disease – CABG favored
- Single vessel – left main coronary artery involved

  ↓

  CABD
- Double vessel – multiple occlusions – CABG

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BASICS AND INTRODUCTION TO ACS

ACS 00:00:46

- Acute coronary syndrome
  - STEMI
  - NSTE-ACS
    - NSTEMI
    - Unstable angina

Based on myocardial necrosis:
- NSTEMI → Biomarker positive
- Unstable angina → Biomarker negative

Pathogenesis 00:04:46

- Atherosclerosis
- 3 Mechanisms
  - Plaque rupture/Fissure
  - Plaque erosion
  - Coronary vasoconstriction

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Ruptured plaque

- Thin fibrous cap

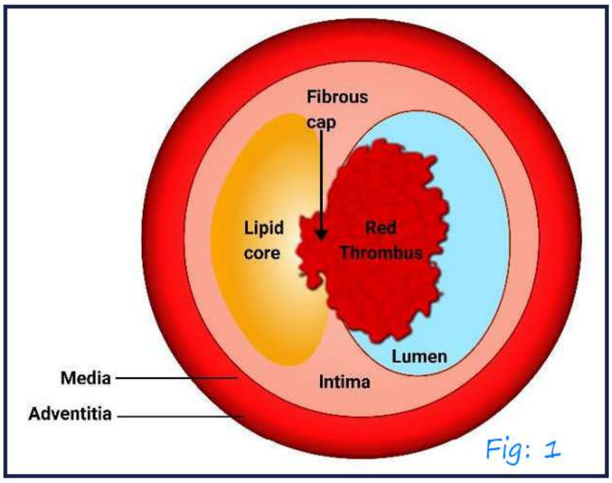

Fig: 1

- Collagen poor fibrous cap
- Large lipid core
- Many macrophages
- Fibrin – Rich thrombus

Eroded plaque

- Proteoglycan glycosaminoglycan rich

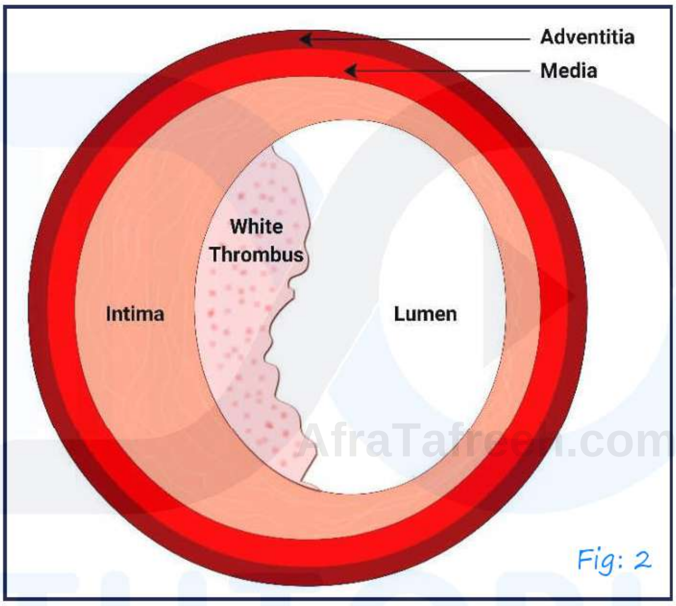

Fig: 2

- Little or no lipid core
- Neutrophiles and NET's
- Many smooth muscle cells
- Platelet – Rich thrombus

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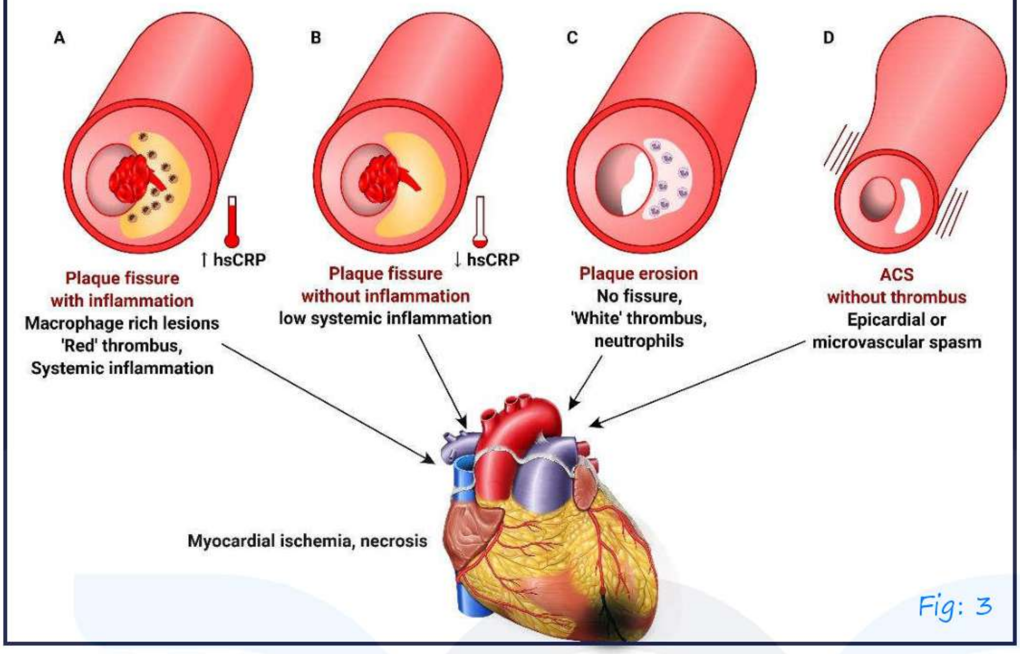


Fig: 3

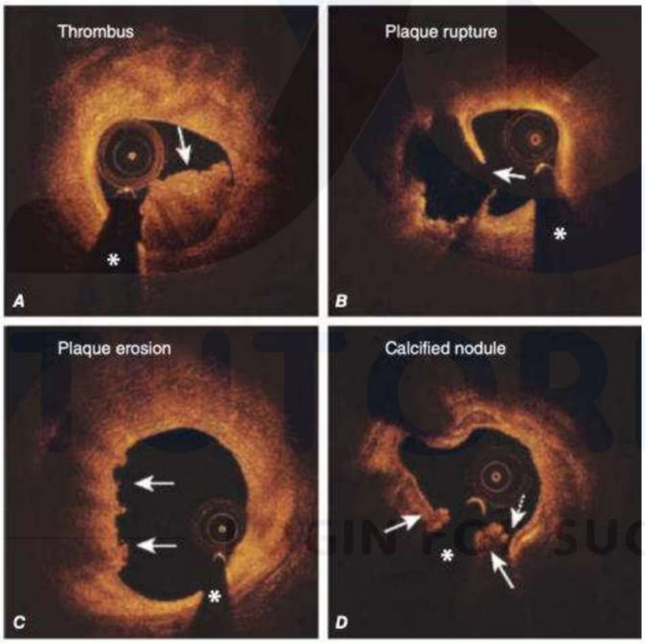


Fig: 4

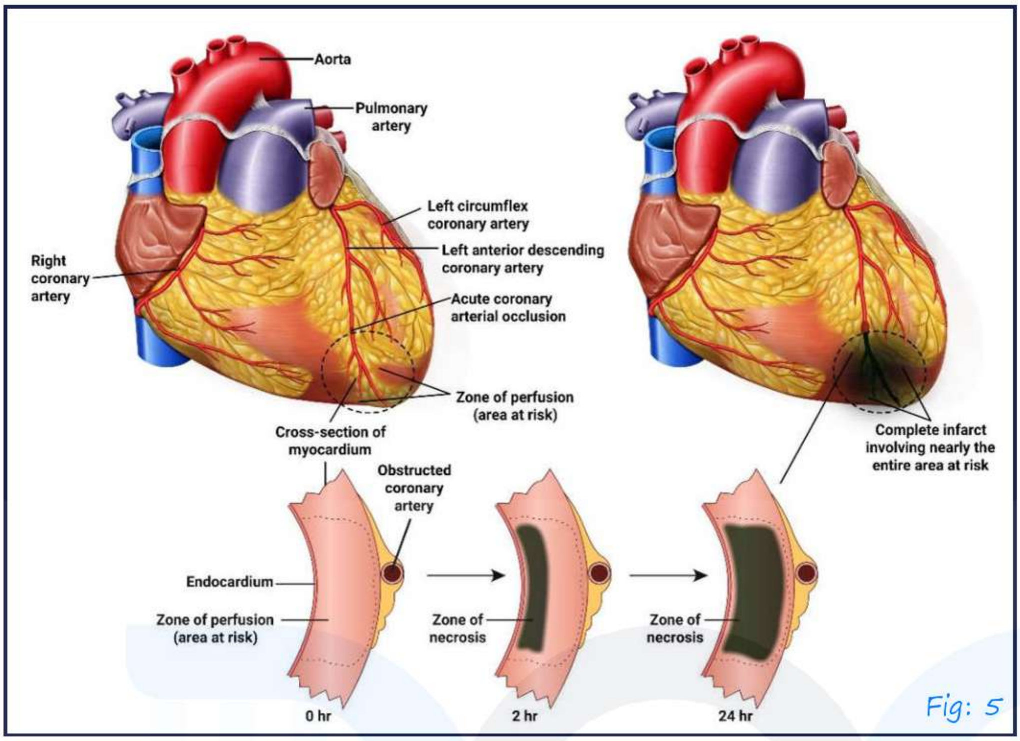
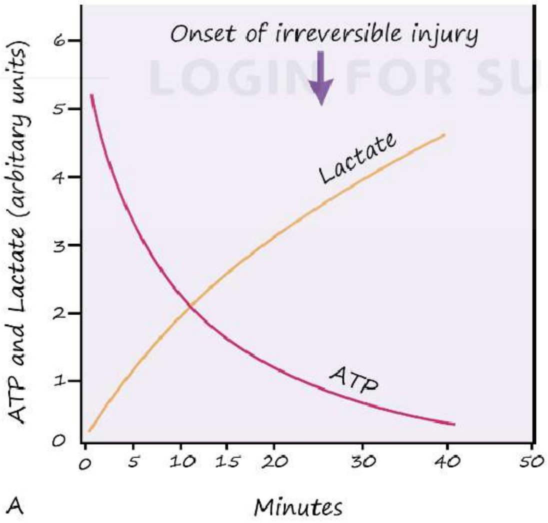


Fig: 5

- Earliest change → Subendocardial ischemia

↓	↓
2hr	Subendocardial necrosis
↓	↓
24hr	Transmural necrosis



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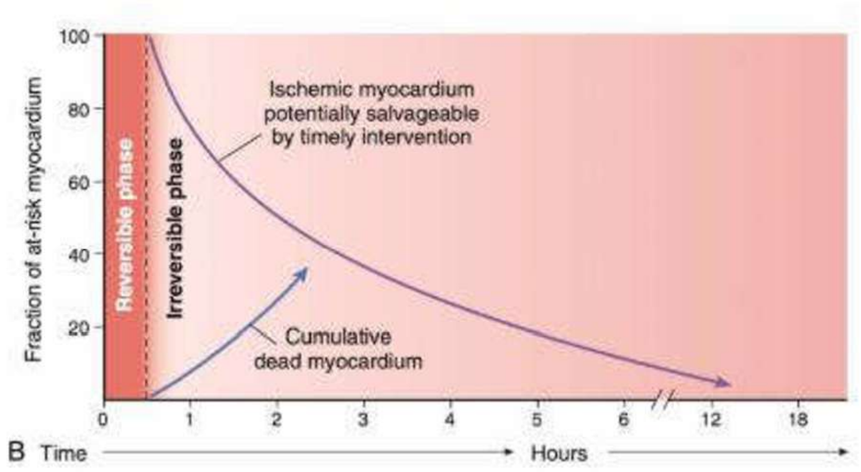

- Initial 30 minutes → reversible phase

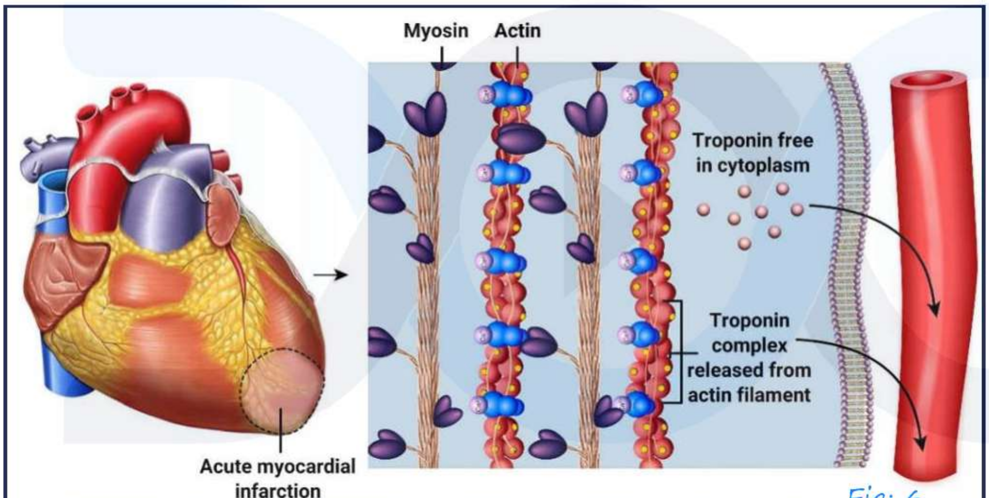

Fig: 6

1. Onset of myocardial infarction
2. Plasma membrane of necrotic myocytes becomes leaky
3. Troponin leaks out of cell into circulation

Cardiac markers 00:22:53

- Heart fatty acid binding protein → earliest (30 mins)
- Myoglobin → 2 hours → less sensitive & specific
- CK-MB

- Troponin - I ⎤ Most specific (I >T)
- Troponin – T ⎦
- LDH
- Best marker for re-infarction Troponin
- Troponin I - 5-10 days
- Troponin T- 10-15 days
- To detect re-infarction= Demonstrate elevation of Troponin in serial blood sample
- 20% increase with a series sample
- LDH
- In individuals – LDH2> LDH1
- In MI – LDH1 > LDH 2
- Copeptin - Recent biomarker

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Causes of elevated of elevated cardiac troponin reflecting direct myocardial damage other than spontaneous myocardial infarction	
Cardiac	Non cardiac or systemic
Tachyarrhythmias	Pulmonary embolism/Pulmonary hypertension
Congestive heart failure	Trauma (e.g. electrical shock, burns, blunt chest wall)
Hypertensive emergencies	Hypo or hyperthyroidism

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Infection/Inflammatory (e.g. myocarditis pericarditis)	Renal failure
Structural heart disease (e.g. aortic stenosis)	Sepsis, shock
Aortic dissection	Stroke or another acute neurologic event
Coronary spasm	Extreme endurance efforts (e.g. ultra-marathon)
Cardiac produces (Endomyocardial biopsy, ablation, CABG, PCI)	Rhabdomyolysis
Infiltrative disease (e.g. amyloidosis hemochromatosis, malignancy)	

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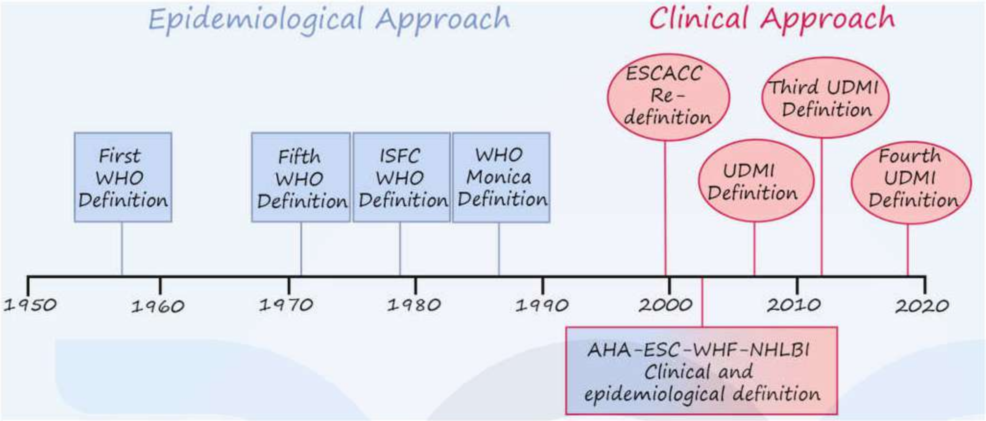
- Now a days → High sensitivity cardiac troponins HS trop I/T

↓

very sensitive.

TYPES OF MYOCARDIAL INFARCTION

Introduction 00:00:43



- 4th UDMI (2018) – Fourth universal definition of myocardial infarction (2018)
- Fourth Universal Definition of Myocardial Infarction (2018)
  - Joint ESC/ACC/AHA/WHF task force for the universal definition of myocardial infarction

Universal definition of myocardial infarction

- Criteria for clinical myocardial infarction
  - Clinical definition of myocardial infarction denotes presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischemia.

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Types of MI 00:08:22

- Type 1
- Type 2
- Type 3
- Type 4 — 4a, 4b, 4c
- Type 5

Type 1

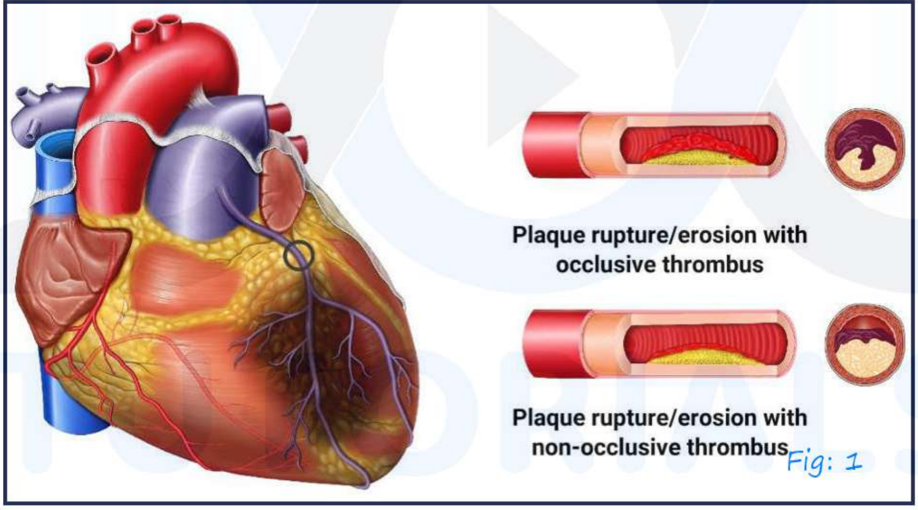

Fig: 1

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- Acute atherothrombotic coronary disease
- Criteria of Type 1 Myocardial Infection

  Detection of a rise and/or fall of cTn with at least one value above the 99th percentile URL and with at least one of the following:

  - Symptoms of acute myocardial ischemia;
  - New ischemic ECG changes;
  - Development of pathological Q waves;

- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic aetiology;
- Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.

Type 2

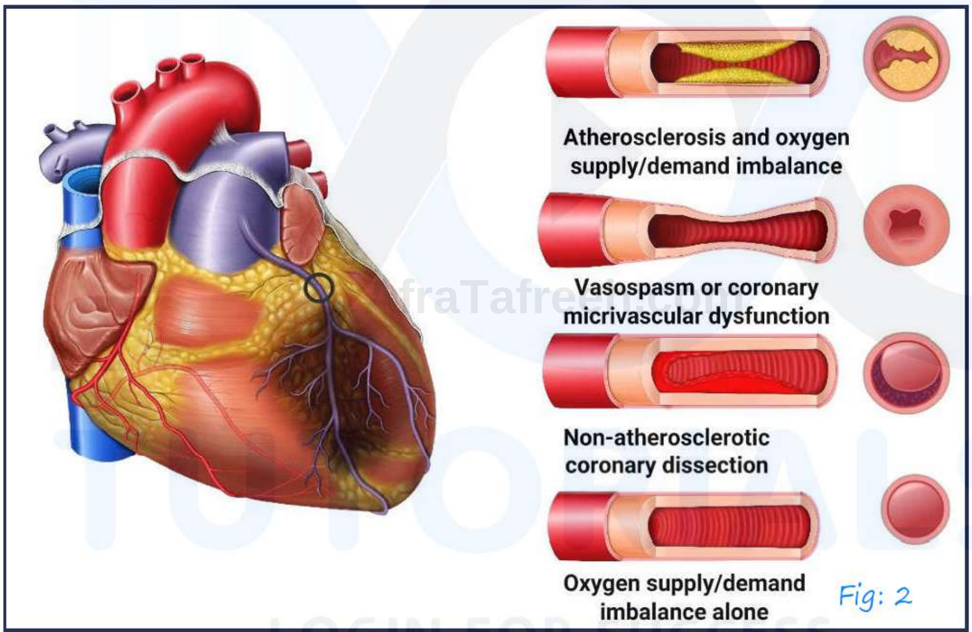

Fig: 2

- Occurs due to mismatch in O_2 supply and demand
- Criteria for Type 2 myocardial infarction
  Detection of a rise and/or fall of c Tn with at least one value above the 99th percentile URL and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary athero-thrombosis, requiring at least one of the following:

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- Symptoms of acute myocardial ischemia;
- New ischemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic a etiology.

Type 3

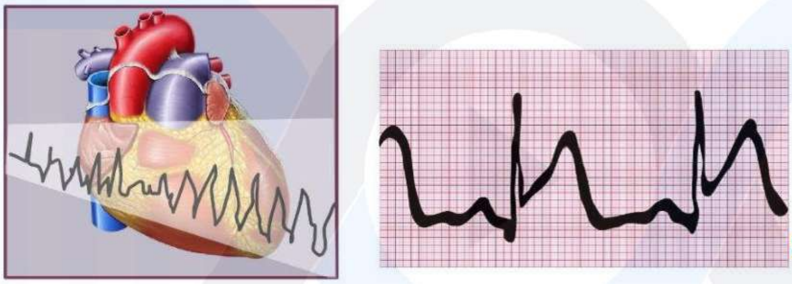
Fig: 3

- Sudden cardiac death
- Criteria for Type 3 Myocardial Infarction
  - Patients who suffer cardiac death, with symptoms suggestive of myocardial ischemia accompanied by presumed new ischemic ECG changes or ventricular fibrillation, but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified or myocardial infarction defected by autopsy examination.

Type 4a

Fig: 4

Percutaneous coronary intervention

Isolated development of new Q waves meets the criteria if c Tn values are elevated and rising but less than the prespecified threshold for PCI

- PCI related MI $\leq$ 48h after the index procedure is defined by elevation of cardiac troponin values > 5 times 99th percentile URL. In addition, either
  - New ischemic ECG changes or
  - Imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality consistent with an ischemic aetiology
  - Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow or distal embolization.

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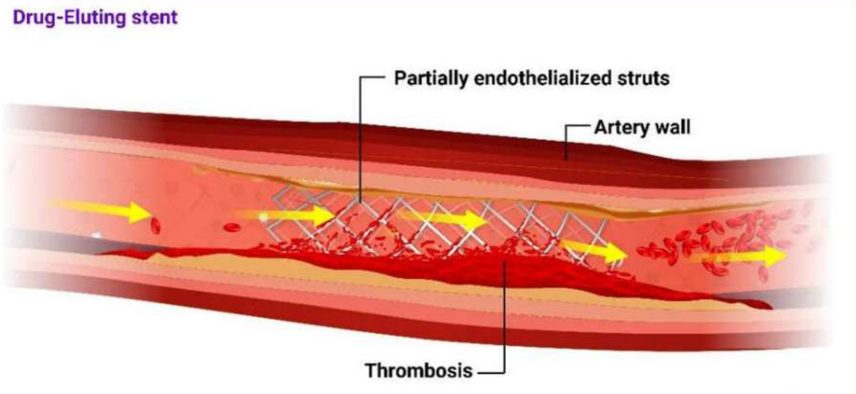
Type 4b



Stent thrombosis

Fig: 5

- Myocardial infarction type 4b
- Myocardial infarction related to stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial is ischemia and with a rise and/or fall or cardiac troponin values with atleast one value > 99th percentile URL. The following temporal categories are suggested:

  – Acute, 0–24 h

  – Subacute >24h to 30 days

  – Late, >30 days to 1 year

  – Very late > 1 year

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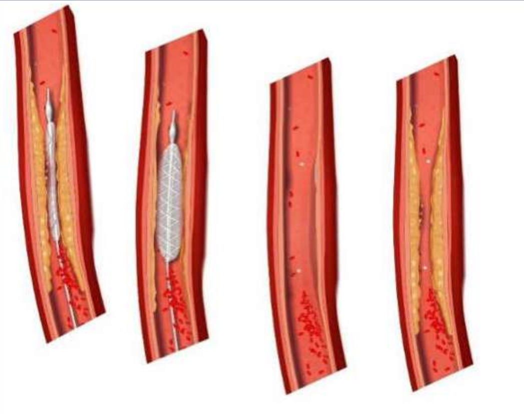
Type 4c



Re-stenosis

Fig: 6

- Myocardial infarction type 4c
  - Myocardial infarction related to stent restenosis, or restenosis following balloon angioplasty in the infarct territory is detected by coronary angiography in the setting of myocardial ischemia and with a rise and/or fall of cardiac troponin values with at least one value > 99th percentile URL
- 4a – PCI related MI ≤ 48 hours
- 4b – Stent thrombosis
- 4c – Re-stenosis

Type 5

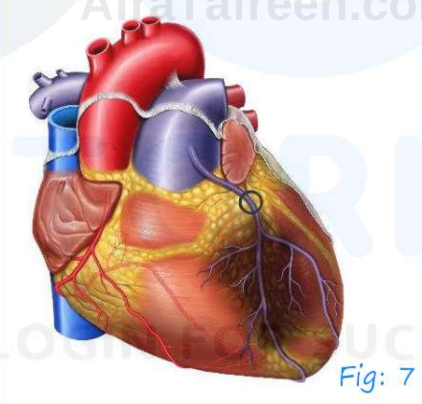


Fig: 7

- Myocardial infarction Type 5

  CABG-related MI _< 48h after the index procedure is defined by elevation of cardiac troponin values >10 times 99th percentile URL. In addition, either
  - new pathological Q waves or
  - angiographic documented new graft or new native coronary artery occlusion, or

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- imaging evidence of new loss of viable myocardium or new regional wall motion abnormality and in a pattern consistent with an ischaemic aetiology.

- Universal definition of myocardial injury
  Criteria for Myocardial injury
  - Detection of elevated cardiac troponin (cTn) values above the 99th percentile upper reference limit (URL) is defined as myocardial injury. The injury is considered acute if there is a rise and/or fall of cTn values.
- Acute myocardial injury – rise/fall of cTn $\geq$ 20%
- Chronic myocardial injury – differential <20%

Elevated Troponin Value(s) > 99th Percentile URL

- Troponin rise and/or fall
- Troponin level stable

Troponin rise and/or fall

- With acute ischaemia → Acute myocardial infarction
  - Atherosclerosis + thrombosis → Type 1 MI: triggers
    - Plaque rupture
    - Plaque erosion
  - Oxygen supply and demand imbalance → Type 2 MI: examples
    - Severe hypertension
    - Sustained tachyarrhythmia
- Without acute ischaemia → Acute myocardial injury → Examples
  - Acute heart failure
  - Myocarditis

Troponin level Stable
↓
Chronic myocardial injury
↓
Examples

- Structural heart disease
- Chronic kidney disease

- Type 1 Myocardial Infarction
  - Spontaneous myocardial infarction related to ischaemia due to primary coronary event such as plaque erosion and/or rupture, fissuring or dissection
- Type 2 myocardial infarction
  - Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply
- Type 3 myocardial infarction
  - Sudden unexpected cardiac death oftern with symptoms suggestive of myocardial ischaemia
- Type 4 myocardial infarction
  - Myocardial infarction associated with percutaneous coronary intervention (4a) or stent thrombosis (4b)
- Type 5 myocardial infarction
  - Myocardial infarction associared with cardiac surgery
- Myocardial injury
  - Multifactorial aetiology; acute or chronic based on change in cardiac troponin concentrations with serial testing.

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EVALUATION AND MANAGEMENT OF STEMI

Introduction 00:00:43

- Unstable angina → no myocardial necrosis
- NSTEMI

2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes

Developed in Collaboration with the Society of Thoracic Surgeons and Society for Cardiovascular Angiography and Interventions

Endorsed by the American Association for Clinical Chemistry

© American College of Cardiology Foundation and American Heart Association

Helping Cardiovascular Professionals Learn. Advance. Heal.

American Heart Association.

ESC European Society of Cardiology — European Heart Journal (2020) 00, 1–79 doi:10.1093/eurheartj/ehaa575 — ESC GUIDELINES

2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)

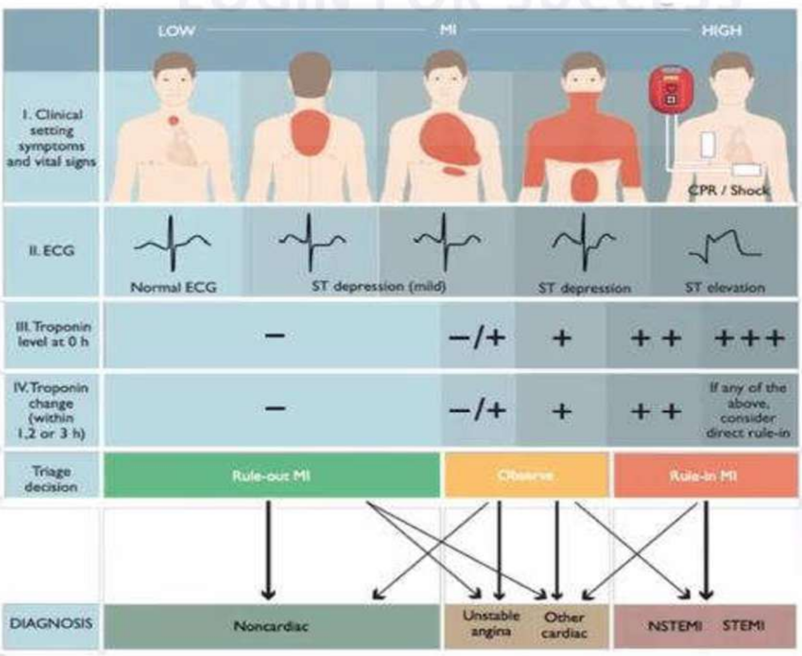

Fig: 1

Clinical features 00:08:24

Clinical features: - NSTE – ACS

- Anginal chest pain
- Pain at rest or minimal exertion
- Pain duration > 10 minutes
- Recent onset pain (within last two weeks)
- Crescendo type pain

Anginal equivalents

- Nausea
- Epigastric discomforts
- Dyspnea

} females, elderly diabetics

O/E: -

- Normal physical examination
- Basal crepts
- S_3

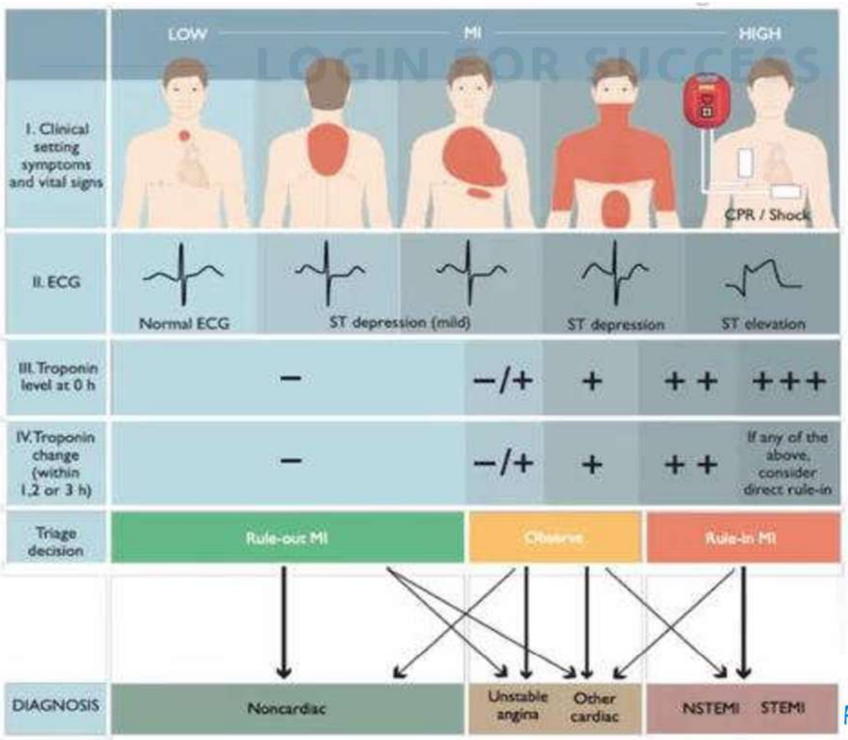

Fig: 2

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ECG: -

- Hyperacute T waves (Earliest)
- ST depression
- T inversion
- First hour: - repeat ECG at 15-30 minutes interval

Electrocardiographic Changes* suggestive of Acute Myocardial Ischaemia
ST-elevation
New ST-elevation at the J-point in two contiguous leads with the cut points: ≥1 mm in all leads other than leads V2- V3, where the following cut points apply ≥2mm in men ≥40 years; ≥2.5 mm in men <40 years, or ≥1.5 mm in women regardless of age.
ST-depression and I wave changes
New horizontal or down-sloping ST-depression ≥0.5 mm in two contiguous leads and/or T inversion >1 mm in two contiguous leads with prominent R wave or R/S ratio> 1.

"In absence of left ventricular hypertrophy and bundle branch block

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Bio markers 00:26:08

- Cardiac troponin I > T
- High sensitivity troponin assays (HS Trop I/ Trop T)
  - 0 hours
  - 1 hours
  - 2 hours
  - 3 hours
- CK – MB

- Co peptin
- Heart fatty acid binding protein
- BNP
- NT – pro BNP

(BNP, NT – pro BNP: Prognostication)

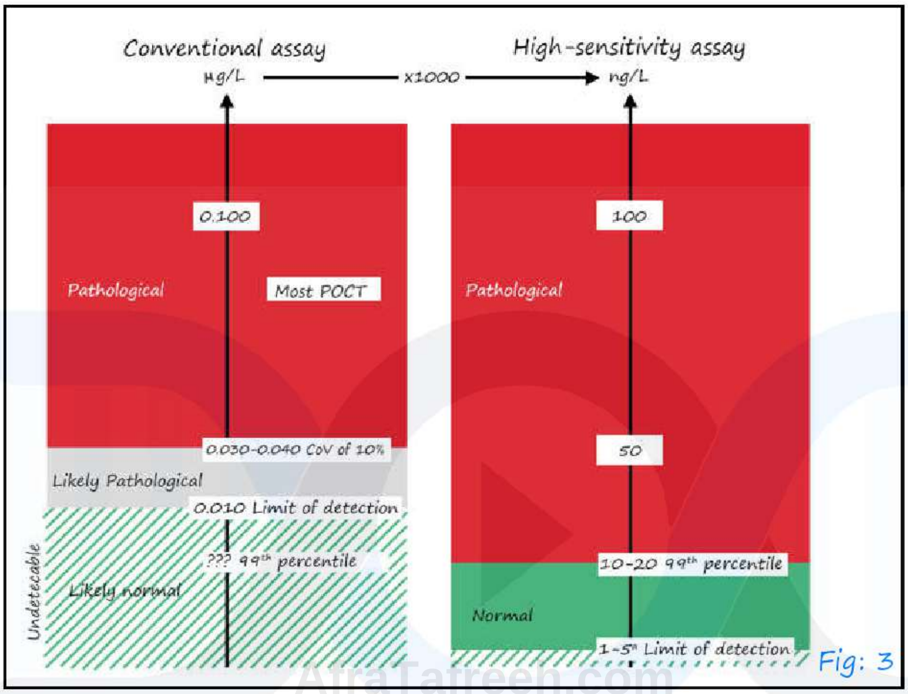

Fig: 3

Conditions other than acute type 1 myocardial infarction associated with cardiomyocyte injury (= cardiac troponin elevation)
Tachyarrhythmias
Heart failure
Hypemergencies
Critical illness (e.g. shock/sepsis/burns)
Myocarditis
Takotsubo syndrome
Valvular heart disease (e.g. aortic stenosis)
Aortic dissection
Pulmonary embolism, pulmonary hypertension
Renal dysfunction and associated cardiac disease

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Acute neurological event (e.g. stroke or subarachnoid hemorrhage)
Cardiac contusion or cardiac procedures (CABG, PCL ablation, pacing, cardioversion, or endomyocardial biopsy)
Hypo- and hyperthyroidism
Infiltrative diseases (e.g. amyloidosis, haemochromatosis, sarcoidosis, scleroderma)
Myocardial drug toxicity or poisoning (e.g. doxorubicin, 5-fluorouracil Herceptin, snake venoms)
Extreme endurance efforts
Rhabdomyolysis

Recommendations for diagnosis, risk stratification, imaging, and rhythm monitoring in patients with suspected non-ST-segment elevation acute coronary syndrome		
Recommendations	Class	level
Imaging		
in patients presenting with cardiac arrest or hemodynamic instability of presumed cardiovascular origin, echocardiography is recommended and should be performed by trained physicians immediately following a 12-lead ECG.	I	C

In patients with no recurrence of chest pain, normal ECG findings, and normal levels of cardiac troponin (preferably high sensitivity), but still with a suspected ACS, a non-invasive stress test (preferably with imaging) for inducible ischemia or CCTA is recommended before deciding on an invasive approach.	I	B

- Coronary CT angiography
- Noninvasive stress test → treadmill testing
  myocardial perfusion scan

ESC Classes of recommendations		
Class	Definition	Wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful	Is not recommended

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ESC Levels of evidence	
Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of evidence B	Data derived from a single randomized clinical trial or large non randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Recommendations for diagnosis, risk stratification, imaging, and rhythm monitoring in patients with suspected non-ST-segment elevation acute coronary syndrome (8)		
Recommendations	Class	level
Imaging		
Rhythm monitoring for >24 h is recommended in NSTEMI patients at increased risk for cardiac arrhythmias.	I	C
In the absence of signs or symptoms of ongoing ischaemia, rhythm monitoring in unstable angina may be considered in selected patients (e.g. suspicion of coronary spasm or associated symptoms suggestive of arrhythmic events).	IIb	C

Recommendations on biomarker measurements for stratification (1) prognostic		
Recommendations	Class	level
Beyond its diagnostic role, it is recommended to measure hs-cTn serially for the estimation of prognosis.	I	B
Measuring BNP or NT-proBNP plasma concentrations should be considered to gain prognostic information.	IIa	B
The measurement of additional biomarkers, such as midregional pro-A-type natriuretic peptide, high-sensitivity C-reactive protein, midregional pro adrenomedullin, GDF-15, copeptin, and h-FABP is not recommended for routine risk or prognosis assessment.	III	B

Recommendations on biomarker measurements for prognost* stratification (2)		
Recommendations	Class	level
Score to risk stratify in NSTE-ACS		
GRACE risk score models should be considered for estimating prognosis.	IIa	B
The use of risk scores designed to evaluate the benefits and risks of different DAPT durations may be considered.	IIb	A
To estimate bleeding risk, the use of scores may be considered in patients undergoing coronary angiography.	IIb	B

Risk scores 01:00:06

Risk scores – prognostication

- Clinical
- ECG
- Biomarkers

(Clinical, ECG) → Grace scoring (ESC); TIMI scoring (AHA/ACC)

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Recommendations on biomarker measurements for prognostic stratification (2)		
Recommendations	Class	level
Score to risk stratify in NSTE-ACS		
GRACE risk score models should be considered for estimating prognosis.	IIa	B
The use of risk scores designed to evaluate the benefits and risks of different DAPT durations may be considered.	IIb	A
To estimate bleeding risk, the use of scores may be considered in patients undergoing coronary angiography.	IIIb	B

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TIMI Risk Score* for NSTE-ACS	
TIMI Risk Score	All-Cause Mortality, New or Recurrent MI, or Severe Recurrent Ischemia Requiring Urgent Revascularization Through 14 d After Randomization, %
0-1	4.7
2	8.3
3	13.2
4	19.9
5	26.2
6-7	40.9

The TIMI risk score is determined by the sum of the presence of 7 variables at admission; 1 point is given for each of the following variables: ≥65y of age: ≥3 risk factors for CAD; prior coronary stenosis ≥50%; ST deviation on ECG: ≥2 anginal events in prior 24 h; use of aspirin in prior 7 d and elevated cardiac biomarkers.

Immediate management 01:05:44

Anti-ischemic therapy

1.Sublingual nitrates (0.3-0.4 mg)

(Buccal spray)

↓

- Can repeat at 5 minutes interval (2-3 doses)
- Always monitor BP

- Nitrates are contra indicated with PDE -5 inhibitors

  ↓

  - Sildenafil within 24 hours
  - Tadalafil within 48 hours

2.IV nitroglycerine infusion

- Watch for hypotension

3.IV morphine

4.Beta blockers within first 24 hours

Beta blockers C/I in severe heart failure

5.Calcium channel blockers

- Verapamil
- Diltiazem

6.Statins

High dose – 80mg

↓

- Pleotropic action
- Plaque stabilization

7.ACE inhibitors/ARB's

- Preferred when EF < 40%
- DM
- Hypertension

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Drugs Commonly Used in Intensive Medical Management of Patients with Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction			
DRUG CATEGORY	CLINICAL CONDITION	WHEN TO AVOID	DOSAGE
Nitrates	Patients with ACS who have chest discomfort or an anginal equivalent	Hypotension Right ventricular infection severe aortic sternosis patient receiving a PDE-5 inhibitor	Initially administer via sublingual or buccal route, and symptoms persist, intravenously Topical or oral nitrates are acceptable alternatives for patients without ongoing or refractory symptoms 5-10 ug/min by continuous infusion started up to 75-100 g/min until relief of symptoms or letting side effects (headache or hypotension with a systolic blood pressure <90 mmHg or >30% below starting mean arterial pressure levels of significant hypertension is present)
Beta blockers	All patients with ACS	PR interval (ECG)>0.24s S or 3 atrioventricular blocks Heart rate <50 beats/minutes Systolic pressure <90mmHg Shock	Metoprolol 25-50 mg by mouth every 6 h if needed, and no heart failure, 5-mg increments by slow (over 1-2 min) Administration

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		Lef5t ventricular failure Severe reactive airway diseases	
Calcium channel blockers	Patients whose symptoms are not relieved by adequate doses of nitrates and beta blockers, or in patients unable to tolerate adequate doses of one or both of these agents patients variant angina	Pulmonary edema Evidence of left ventricular dysfunction (for diltiazem or verapamil)	Dependent on specific agent
Morphine sulphate	Patients whose symptoms are not relieved after three serial sublingual nitroglycerin tablets or whose symptoms recur with adequate anti ischemic therapy	Hypotension Respiratory depression Confusion Obtundation	2-5 mg IV dose May be repeated every 5-30 min as needed to relieve symptoms and maintain patient comfort

Anti-thrombotic therapy

- Anti thrombotic therapy divided into two types: -

  1.Antiplatelet

  2.Anticoagulant

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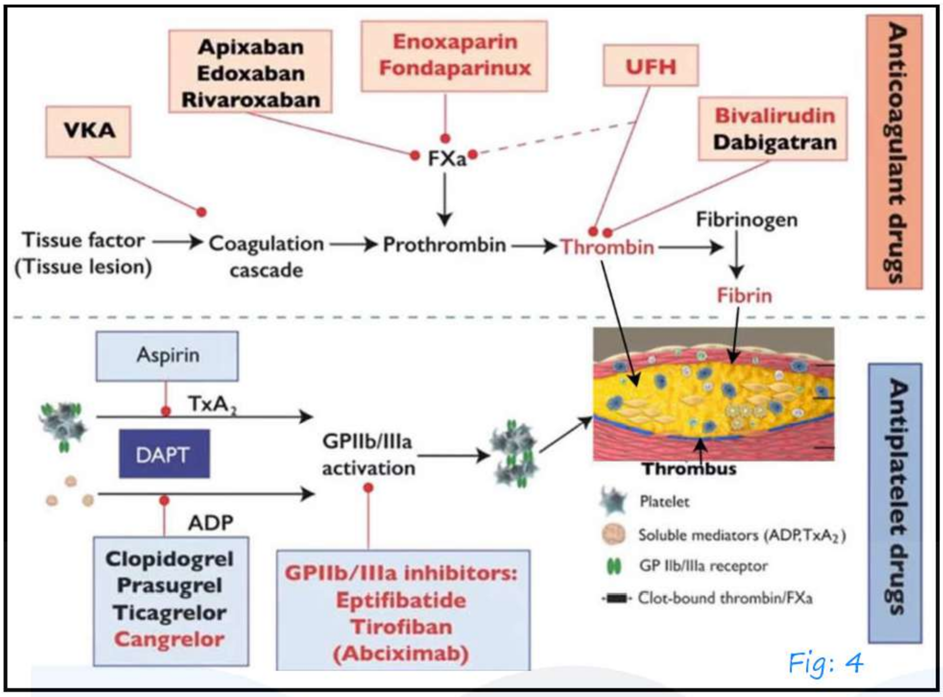

Fig: 4

P_2y12 inhibitors

- Clopidogrel
- Prasugrel
- Ticagrelor
- Cangrelor

Clinical Use of Antithrombotic Therapy	
Oral Antiplatelet Therapy	
Aspirin Clopidogrel prasugrel Ticagrelor	Initial dose of 325 mg nonenteric formulation followed by 75-100 mg/d of an enteric or a nonenteric formulation Loading dose of 300-600 mg followed by 75 mg/d Pre-PCI: Load ng followed by 10 mg/d Loading dose of 180 mg followed by 90 mg twice daily
Intravenous Antiplatelet Therapy	

abciximab Eptifibatide Tirofiban Cangrelor	0.25 mg followed by infusion of 0.125 ug/ kg per min (maximum 10 ug/min) for 12-24 h 180 µg/kg bolus followed 10 min later by second bolus of 180 ug with infusion of 2.0 ug/kg per min for 72-96 h following first bolus 25 µg/kg per min followed by infusion of 0.15 µg/kg per min for 48-96 h 30 ug/kg bolus followed immediately by a 4 ug/kg per min infusion
Anticoagulants	
Unfractionated heparin (UFH) Enoxaparin Fondaparinux	Bolus 70-100 U/kg (maximum 5000 U) IV followed by infusion of 12-15 U/kg per h (initial maximum 1000 U/h) titrated to ACT 250-300 s 1 mg/kg SC every 12 h; the first dose may be preceded by a 30-mg IV bolus; renal adjustment to 1 mg/kg once daily if creatine clearance <30 mL/min 2.5 mg SC qd Initial Iv bolus of 0.75 mg/kg and an infusion of 1.75mg/kg per h

Antiplatelets

- Aspirin – 300mg loading dose
  75mg maintenance dose
- Clopidogrel → 600mg loading dose
  90mg BD maintenance dose

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- Ticagrelor → 180mg loading dose
  90 mg BD maintenance dose

- Prasugrel → 60mg loading dose
  10mg maintenance dose
  Preferred when going for PCI
- Cangrelor
- Ticagrelor prasugrel → more potent than clopidogrel
  ↓
  Increase risk of bleeding

IV GP II b/III a inhibitors

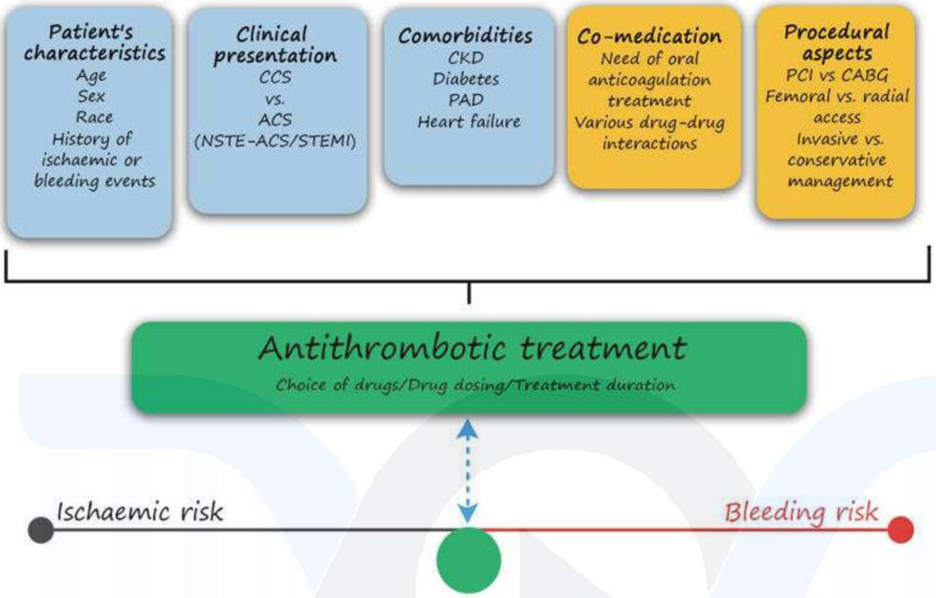
- Abciximab
- Eptifibatide
- Throfiban

(Abciximab, Eptifibatide, Throfiban) — High risk patient taken for PCI

Anticoagulants

Unfractionated heparin (UFH)	Bolus 70-100 U/kg (maximum 5000 U) IV followed by infusion of 12-15 U/lg per h (initial maximum 1000 U/h) titrated to ACT 250-300 s
Enoxaparin	1 mg/kg SC every 12h; the first dose may be preceded by a 30 mg IV bolus; renal adjustment of 1mg/kg once daily if creatine clearance <30 mL/min

Fondaparinux	2.5 mg SC qd
Bivalirudin	Initial IV bolus of 0.75 mg/kg and an infusion of 1.75 mg/kg per h



Revascularization

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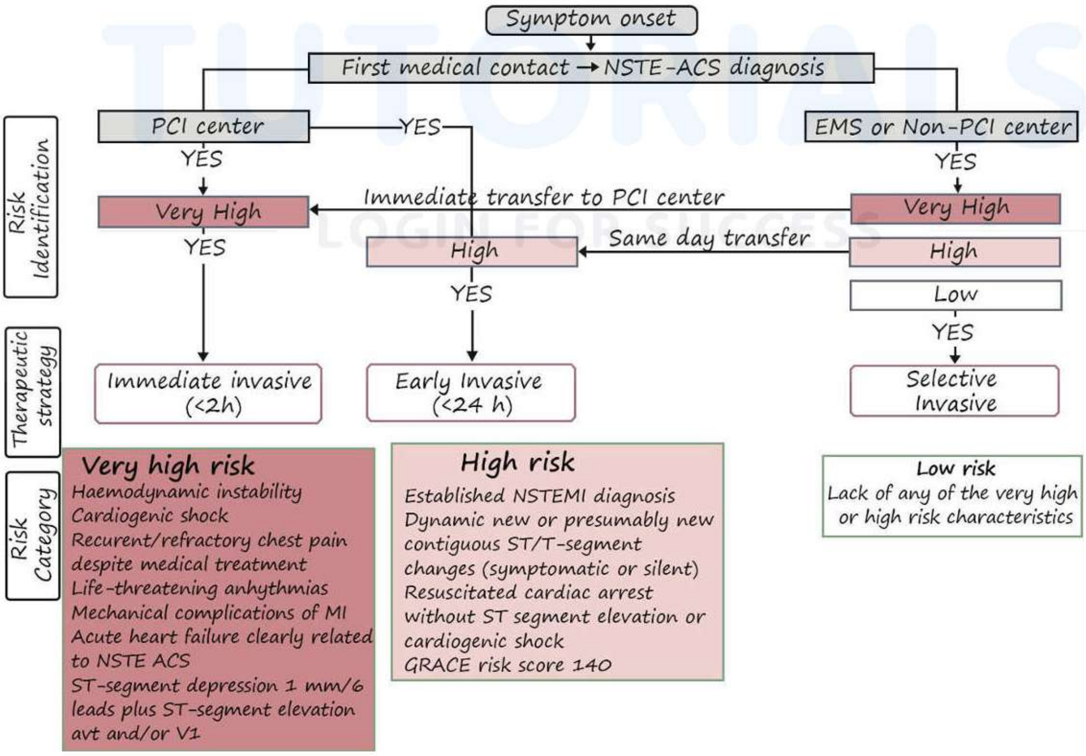

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- NSTE – ACS

  ↓

  Low TIMI and grace score

  ↓

  Unstable angina

  ↓

  Medical management → ischemia guided strategy

Initial Treatment

- DAPT and Anticoagulant therapy

  1. Aspirin (COR I, LOE A).
  2. P2Y12 inhibitor clopidogrel or ticagrelor (COR I, LOE B).
  3. Anticoagulant:

     Enoxaparin (COR I, LOE A) or UFH (COR I, LOE B) or fondaparinux (COR I, LOE B) or bivalirudin (for early invasive strategy, COR I. LOE B).
  4. Can consider GP IIBIIIA receptor inhibitors in high-risk patients stratified to early invasive strategy (eptifibatide or tirofiban; COR IIb. LOE B).

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During hospitalization

- Medically treated patients: 1. Aspirin (COR I, LOE A).

  1. aspirin (COR I, LOE A).
  2. P2Y 12 inhibitor, either ticagrelor or clopidogrel (COR I, LOE B).
  3. anticoagulant:

     Enoxaparin (COR I, LOE A) or UFH (CORI, LOE B) or fondaparinux (CORI, LOE B).

- PCI treated patients:
  1. Aspirin (COR I. LOE A).
  2. P2Y 12: inhibitor: clopidogrel or ticagrelor or prasugrel
     (COR I, LOE B).:
  3. anticoagulant:
     Enoxaparin (COR I, LOE A) or UFH (CORI, LOE B) or fondaparinux (COR I, LOE B) or bivalirudin (CORI, LOE B).
  4. Can consider GP IIb, IIIa receptor inhibitors in high-risk patients not adequately per- treated with clopidogrel (COR I, LOE A) or in high-risk patients adequately pre-treated with clopidogrel (COR IIa. LOE B).

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Long-term

- Medically treated patients:
  1. Aspirin indefinitely (COR I, LOE A).
  2. P2Y 12 inhibitor: clopidogrel or ticagrelor for up to 12 months (COR I. LOE B)
- PCI treated patients:
  1. Aspirin indefinitely (COR I, LOE A).
  2. P2Y 12 inhibitor clopidogrel or ticagrelor or prasugrel for at least 12 months (COR I, LOE B).
- Aspirin 75mg
  Clopidogrel 75 mg
  } Dual antiplatelets for 12 months
- After 12 months, aspirin alone lifelong

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Summary

- Unstable angina and NSTEMI – same management [ESC 2020-ACC/AHA 2014]
- Initial evaluation and risk stratification in emergency department
- Immediate management
- Antithrombotic
- Revascularization.

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MANAGEMENT OF STEMI

Introduction 00:00:20

- ST Elevation occurs when there is total occlusion or partial occlusion

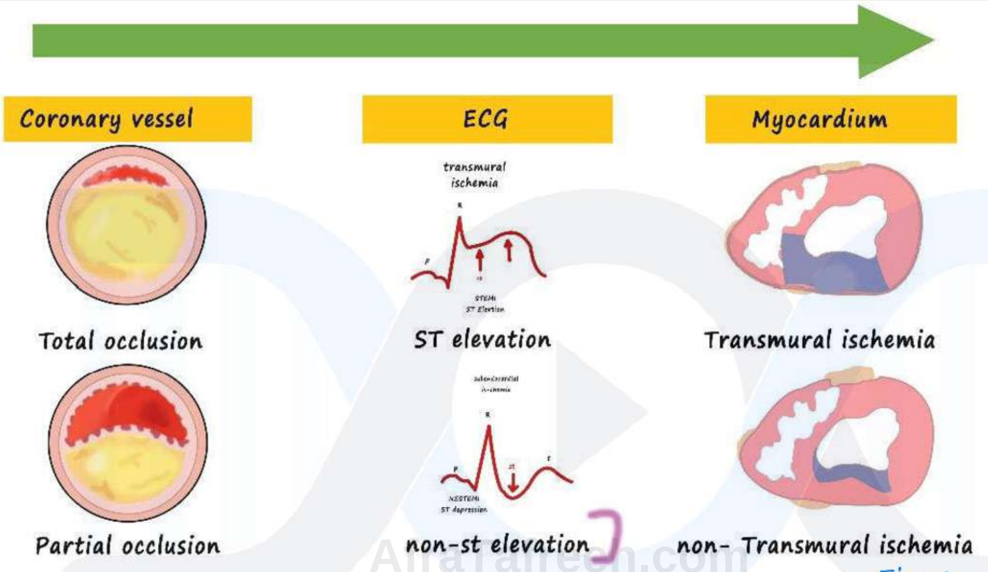

Fig: 1

Guidelines 00:03:15

- Clinical features similar to non-ST elevation MI
  - 2017 ESC guidelines

2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

-Classes of recommendations

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Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and / or general agreement that a given treatment or procedure is beneficial, useful, effective.	is recommended / is indicated.
Class II	Conflicting evidence and / or a divergence of opinion about the usefulness / efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence / opinion is in favour of usefulness / efficacy.	Should be considered.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered.
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended.

- Level of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.

Level of evidence G	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

- FMC – First medical count
- STEMI diagnosis – ECG alone
- Within 10 min of FMC, the diagnosis must be done
- PCI - percutaneous coronary intervention

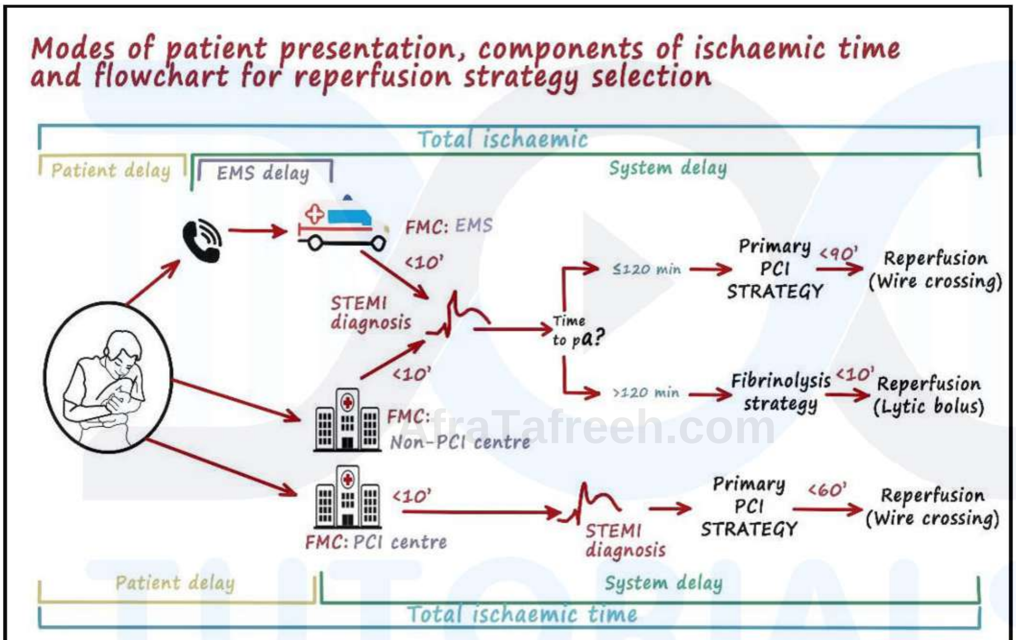

Fig: 2

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Fibrinolysis

- Tenecteplase
- Alteplase
- Reteplase
  - Initial diagnosis

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Recommendations	Class	Level
ECG monitoring		
12-lead ECG recording and interpretation is indicated as soon as possible at the point of FMC, with a maximum target delay of 10 min.	I	B
ECG monitoring with defibrillator capacity is indicated as soon as possible in all patients with suspected STEMI	I	B
The use of additional posterior chest wall leads (V7-V9) in patients with high suspicion of posterior myocardial infarction (circumflex occlusion) should be considered.	IIa	B
The use of additional right precordial leads (V3R and V4R) in patients with inferior myocardial infarction should be considered to identify concomitant RV infarction.	IIa	B
Blood sampling		
Routine blood sampling for serum markers is indicated as soon as possible in the acute phase but should not delay reperfusion treatment.	I	C

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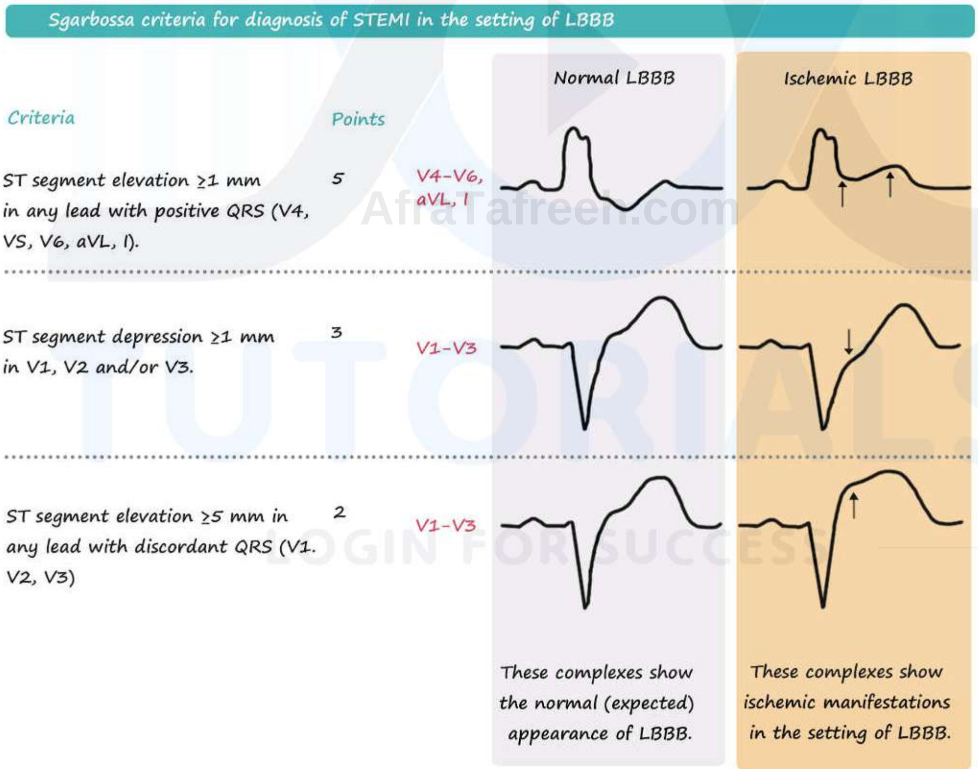
- Electrocardiographic Changes suggestive of Acute Myocardial Ischemia

ST-elevation
New ST-elevation at the J-point in two contiguous leads with the cut points: ≥ 1mm in all leads other than leads V2-V3 where the following cut points apply >2mm in men ≥40 years; ≥2.5 mm in men <40 years, or ≥1.5 mm in women regardless of age.

- > 1mm – in all leads other than V_2 and V_3
  - Males < 40 years → ≥ 2.5mm
  - Males ≥ 40 years → ≥ 2mm
  - Females 40 years → ≥ 1.5mm

  } significant ST elevation



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- Relief of hypoxemia and symptoms

Recommendations	class	Level
Hypoxia		
Oxygen is indicated in patients with hypoxaemia (SaO_2 <90% or PaO_2 <60 mmHg).	I	C
Routine oxygen is not recommended in patients with $SaO_2 \geq 90\%$.	III	B
Symptoms		
Titrated i.v. opioids should be considered to relieve pain.	IIa	C
A mild tranquillizer (usually a benzodiazepine) should be considered in very anxious patients.	IIa	C

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- Definitions of terms related to reperfusion therapy

Term	Definition
FMC	The time point when the patient is either initially assessed by a physician, paramedic, nurse or other trained EMS personnel who can obtain and interpret the ECG, and deliver initial interventions (example defibrillation). FMC can be either in the prehospital setting or upon patient arrival at the

	hospital (example emergency department).
STEMI diagnosis	The time at which the ECG of a patient with ischemic symptoms is interpreted as presenting ST-segment elevation or equivalent.
Primary PCI	Emergent PCI with balloon, stent, or other approved device, performed on the IRA without previous fibrinolytic treatment.

Term	Definition
Primary PCI strategy	Emergent coronary angiography and PCI of the IRA if indicant
Rescue PCI	Emergent PCI performed as soon as possible in the case of failed fibrinolytic treatment.
Routine early PCI strategy after fibrinolysis	Coronary angiography, with PCI of the IRA if indicated, performed between 2 and 24 hours after successful fibrinolysis.
Pharmacoinvasive strategy	Fibrinolysis combined with rescue PCI (in case of failed fibrinolysis) or routine early PCI strategy (in case of successful fibrinolysis).

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- Failed fibrinolysis → < 50% reduction is ST elevation (or) persisting symptoms → Rescue PCL

Reperfusion strategies in the infarct-related artery according to time from symptoms onset

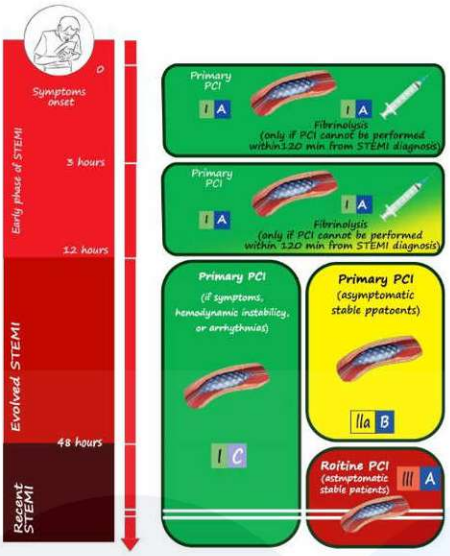

Fig: 3

- Early onset of STEMI → 0-12 hours
- Evolved STEMI → 12 hours – 48 hours
- Recent STEMI → (>48 hours)

Reperfusion strategies in the infarct-related artery according to time from symptoms onset

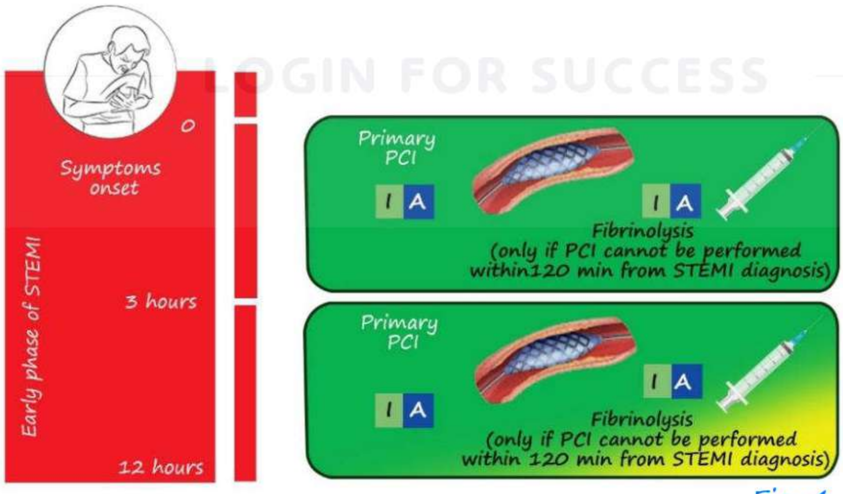

Fig: 4

Reperfusion strategies in the infarct-related artery according to time from symptoms onset (continued)

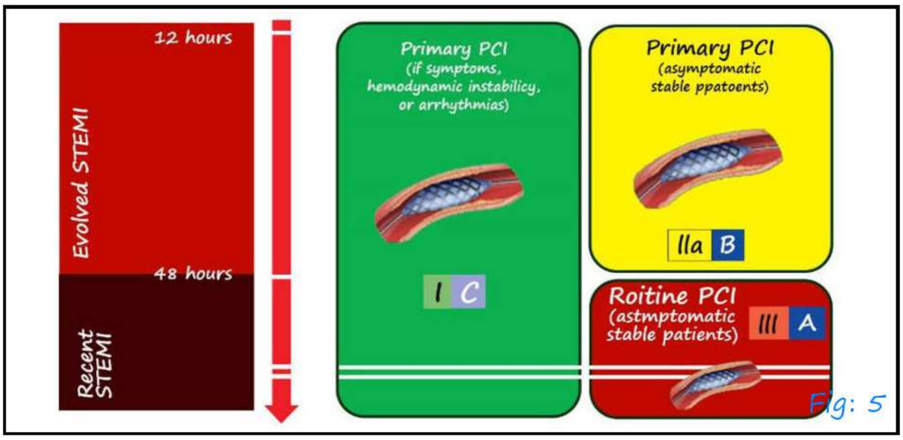

Fig: 5

- Beyond 12 hours of onset → no fibrinolysis
- Beyond 48 hours (if asymptomatic) → No PCI ssss

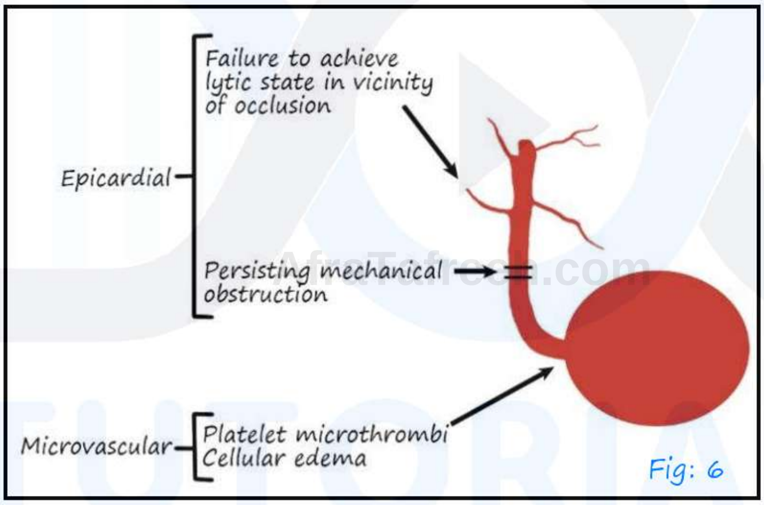

Fig: 6

Failed fibrinolyis

- Reperfusion therapy

Recommendations	Class	level
Reperfusion therapy is indicated in all patients with symptoms of ischemia of ≤12 hours duration and persistent ST-segment elevation.	I	A

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A primary PCI strategy is recommended over fibrinolysis within indicated time frames.	I	A
If primary PCI cannot be performed timely after STEMI diagnosis, fibrinolytic therapy is recommended within 12 hours of symptom onset in patients without contra-indications.	I	A

- Reperfusion therapy (continued)

Recommendations	Class	Level
In the absence of ST-segment elevation, a primary PCI strategy is indicated in patients with suspected ongoing ischemic symptoms suggestive of myocardial infarction and at least one of the following criteria presents: - hemodynamic instability or cardiogenic shock, - recurrent or ongoing chest pain refractory to medical treatment, - life-threatening arrhythmias or cardiac arrest, - mechanical complications of myocardial infarction, - acute heart failure,	I	C

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- recurrent dynamic ST-segment or T-wave changes, particularly with intermittent ST-segment elevation.		

- Procedural aspects of the primary percutaneous coronary intervention strategy

Recommendations	Class	Level
IRA strategy		
Primary PCI of the IRA is indicated.	I	A
New coronary angiography with PCI if indicated is recommended in patients with symptoms or signs of recurrent or remaining ischemia after primary PCI.	I	C
IRA technique		
Stenting is recommended (over balloon angioplasty) for primary PCI.	I	A
Stenting with new-generation DES is recommended over BMS for primary PCI.	I	A
Radial access is recommended over femoral access if performed by an experienced radial operator.	I	A

- Procedural aspects of the primary percutaneous coronary intervention strategy

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Recommendations	Class	Level
IRA technique (continued)		
Routh use of thrombus aspiration is not recommended.	III	A
Routine use of deferred stenting is not recommended.	III	B
Non-IRA strategy		
Routine revascularization of non-IRA lesions should be considered in STEMI patients with multivessel disease before hospital discharge.	IIa	A
Non-IRA PCI during the index procedure should be considered in patients with cardiogenic shock.	IIa	C
CABG should be considered in patients with ongoing ischemia and large areas of jeopardized myocardium if PCI of the IRA cannot be performed.	IIa	C

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- Periprocedural and postprocedural antithrombotic therapy in patients undergoing primary percutaneous coronary intervention

Recommendations	Class	level
Antiplatelet therapy		
A potent P2Y12 inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contra-indicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months unless there are contra-indications such as excessive risk of bleeding.	I	A
Aspirin (oral or i.v, if unable to swallow) is recommended as soon as possible for all patients without contra-indications.	I	B
GP IIb/IIIa inhibitors should be considered for bailout if there is evidence of no-reflow or a thrombotic complication.	IIa	C
Cangrelor may be considered in patients who have not received P2Y12 receptor inhibitors.	IIb	A

- Periprocedural and postprocedural antithrombotic therapy in patient undergoing prima cutaneous coronary intervention

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Recommendations	class	level
Anticoagulant therapy		
Anticoagulation is recommended for all patients in addition to antiplatelet therapy during primary PCI.	I	C
Routine use of UFH is recommended.	I	C
In patients with heparin-induced thrombocytopenia, bivalirudin is recommended as the anticoagulant agent during primary PCI.	I	C
Routine use of enoxaparin i.v. should be considered.	IIa	A
Routine use of bivalirudin should be considered.	IIa	A
Fondaparinux is not recommended for primary PCI.	III	B

- Doses of antiplatelet and anticoagulant co-therapies in primary PCI

Doses of antiplatelet and parenteral anticoagulant co-therapies in primary PCI	
Antiplatelet therapies	
Aspirin	Loading dose of 150-300 mg orally or of 75-250 mg i.v. if oral ingestion is not possible, followed by a maintenance dose of 75-100 mg/day.

Clopidogrel	Loading dose of 600 mg orally, followed by a maintenance dose of 75 mg/day.
Prasugrel	Loading dose of 60 mg orally, followed by a maintenance dose of 10 mg/day. In patients with body weight ≤60 kg, a maintenance dose of 5 mg/day is recommended. Prasugrel is contra-indicated in patients with previous stroke. In patients ≥75 years, prasugrel is generally not recommended, but a dose of 5 mg/day should be used if treatment is deemed necessary.

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- Doses of antiplatelet and anticoagulant co-therapies in primary PCI (continued)

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Doses of antiplatelet and parenteral anticoagulant co-therapies in primary PCI	
Antiplatelet therapies (continued)	
Ticagrelor	Loading dose of 180 mg orally, followed by a maintenance dose of 90 mg b.i.d
Abciximab	Bolus of 0.25 mg/kg i.v. and 0.125 μg/kg/min infusion (maximum 10 μg/min) for 12 hours
Eptifibatide	Double bolus of 180 μg/kg i.v. (given at a 10-min interval) followed by an

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	infusion of 2.0 ug/kg/min for up to 18 hours.
Tirofiban	25 µg/kg over 3 min i.v., followed by a maintenance infusion of 0.15 µg/kg/min for up to 18 hours.

- Doses of antiplatelet and anticoagulant co-therapies in primary PCI(continued)

Doses of antiplatelet and parenteral anticoagulant co-therapies in primary PCI	
Parenteral anticoagulant therapies	
UFH	70-100 IU/kg i.v. bolus when no GP IIb/IIIa inhibitor is planned 50-70 IU/kg i.v. bolus with GP IIb/IIIa inhibitors.
Enoxaparin	0.5 mg/kg i.v. bolus.
Bivalirudin	0.75 mg/kg i.v. bolus followed by i.v. infusion of 1.75 mg/kg/hour for up to 4 hours after the procedure.

- Fibrinolytic therapy

Recommendations	Class	Level
When fibrinolysis is the reperfusion strategy, it is recommended to initiate this treatment as soon as possible after STEM diagnosis, preferably in the prehospital setting.	I	A

A fibrin-specific agent (i.e. tenecteplase, alteplase, reteplase) is recommended.	I	B
A half-dose of tenecteplase should be considered in patients ≥75 years of age.	IIa	B
Antiplatelet co-therapy with fibrinolysis		
Oral or i.v. aspirin is indicated.	I	B
Clopidogrel is indicated in addition to aspirin.	I	A
DAPT (in the form of aspirin plus a P2Y12 inhibitor) is indicated for 12 up to 1 year in patients undergoing fibrinolysis and subsequent PCI.	I	C

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- Fibrinolytic therapy (continued)

Recommendations	Class	Level
Anticoagulation co-therapy with fibrosis		
Anticoagulation is recommended in patients treated with lyrics until revascularization (if performed) or for the duration of hospital stay up to 8 days. The anticoagulant can be:	I	A
Enoxaparin i.v. followed by s.c. (preferred over UFH).	I	A
- UFH given as a weight-adjusted i.v. bolus followed by infusion.	I	B
In patients treated with streptokinase: fondaparinux i.v. bolus	IIa	B

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followed by an s.c. dose 24 hours later.		
Transfer after fibrinolysis		
Transfer to a PCI-capable center following fibrinolysis is indicated in all patients immediately after fibrinolysis.	I	A

- Fibrinolytic therapy (continued)

Recommendations	Class	Level
Interventions following fibrinolysis		
Emergency angiography and PCI if indicated is recommended in patients with heart failure/shock.	I	A
Rescue PCI is indicated immediately when fibrinolysis has failed (<50% ST-segment resolution at 60-90 min) or at any time in the presence of hemodynamic or electrical instability, or worsening ischemia.	I	A
Angiography and PC of the IRA, if indicated, is recommended between 2 and 24 hours after successful fibrinolysis.	I	A
Emergency angiography and PCI if needed is indicated in the case of recurrent ischemia or evidence of reocclusion after initial successful fibrinolysis.	I	B

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Dosing schedule

- Doses of fibrinolytic agents and antithrombotic co-therapies

Drug	Initial treatment	Specific contra-indications
Doses of fibrinolytic therapy		
Streptokinase	1.5 million units over 30-60 min i.v.	Previous treatment with streptokinase or anistreplase
Alteplase (tPA)	15 mg Lv. bolus 0.75 mg/kg iv. over 30 min (up to 50 mg) then 0.5 mg/kg iv over 60 min (up to 35 mg)	
Reteplase (TPA)	10 units + 10 units iv bolus given 30 min apart	
Tenecteplase (TNK-LPA)	Single i.v. bolus: 30 mg (6000 IU) if <60 kg 35 mg (7000 IU) if 60 to <70 kg 40 mg (8000 IU)if 70 to <80 kg 45 mg (9000 IU) if 80 to <90 kg 50 mg (10000 IU) if ≥90 kg It is recommended to reduce to half dose in patients ≥75 years of age.	

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Fibrinolytic agent	Dose	Fibrin specifi-city	Fibrinogen depletion	Antigenic	Patency rate (90-min time 2 or 3. Flow)
Fibrin Specific					
Tenecteplase (TNK)	Singls IV weight-based boles	++++	Minimal	No	85%
Reteplase (r-PA)	10 units + 10-unit IV boluses given 30 min apart	++	Moderate	No	84%
Alteplase (t-PA)	90-min weight-based infusion	++	Mild	No	73-84%
Non-Fibrin Specific					
streptokinase	1.5million units over 30-60 min	No	Marked	Yes	60-68%

- Doses of fibrinolytic agents and antithrombotic co-therapies (continued)

Drug	Initial treatment	Specific contra-indications
Doses of antiplatelet co-therapies		
Aspirin	Starting dose of 150-300 mg orally (or 75-250 mg intravenously if oral ingestion is not possible), followed by a maintenance dose of 75-100 mg/day	
Clopidogrel	Loading dose of 300 mg orally, followed by a maintenance dose of 75 mg/day. In patients >75 years of age: loading dose of 75 mg, followed by a maintenance dose of 75 mg/day	

- Doses of fibrinolytic agents and antithrombotic co-therapies (continued)

Drug	Initial treatment	Specific contra-indications
Doses of fibrinolytic therapy		
Enoxaparin	In patients <75 years of age: 30 mg i.v. bolus followed 15 min later by1 mg/kg s.c. every 12 hours until	

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	revascularization or hospital discharge for a maximum of 8 days. The first two s.c. doses should not exceed 100 mg per injection.	
	In patients >75 years of age: no i.v. bolus; start with first s.c. dose of 0.75 mg/kg with a maximum of 75 mg per injection for the first two s.c. doses. In patients with eGFR <30 ml/min/1.73 m², regardless of age, the s.c. doses are given once every 24 hours.	

- Doses of fibrinolytic agents and antithrombotic co-therapies (continued)

Drug	Initial treatment	Specific contra-indications
UFH	60 IU/kg i.v. bolus with a maximum of 4000 IU followed by an i.v. infusion of 12 IU/kg with a maximum of 1000 IU/hour for 24-48 hours. Target aPTT: 50-70s or 1.5 to 2.0 times that of control to be monitored at 3, 6, 12 and 24 hours.	

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Fondaparinux (only with streptokinase)	2.5 mg i.v. bolus followed by a s.c. dose of 2.5 mg once daily up to 8 days or hospital discharge.	

- Contra-indications to fibrinolytic therapy

Absolute
Previous intracranial hemorrhage or stroke of unknown origin at any time.
Ischemic stroke in the preceding 6 months.
Central nervous system damage or neoplasms or arteriovenous malformation.
Recent major trauma/surgery/head injury (within the preceding month).
Gastrointestinal bleeding within the past month.
Known bleeding disorder (excluding menses).
Aortic dissection.
Non-compressible punctures in the past 24 hours (example: liver biopsy, lumbar puncture).

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- Contra-indications to fibrinolytic therapy

Relative
Transient ischemic attack in the preceding 6 months.
Oral anticoagulant therapy.
Pregnancy or within 1 week postpartum.

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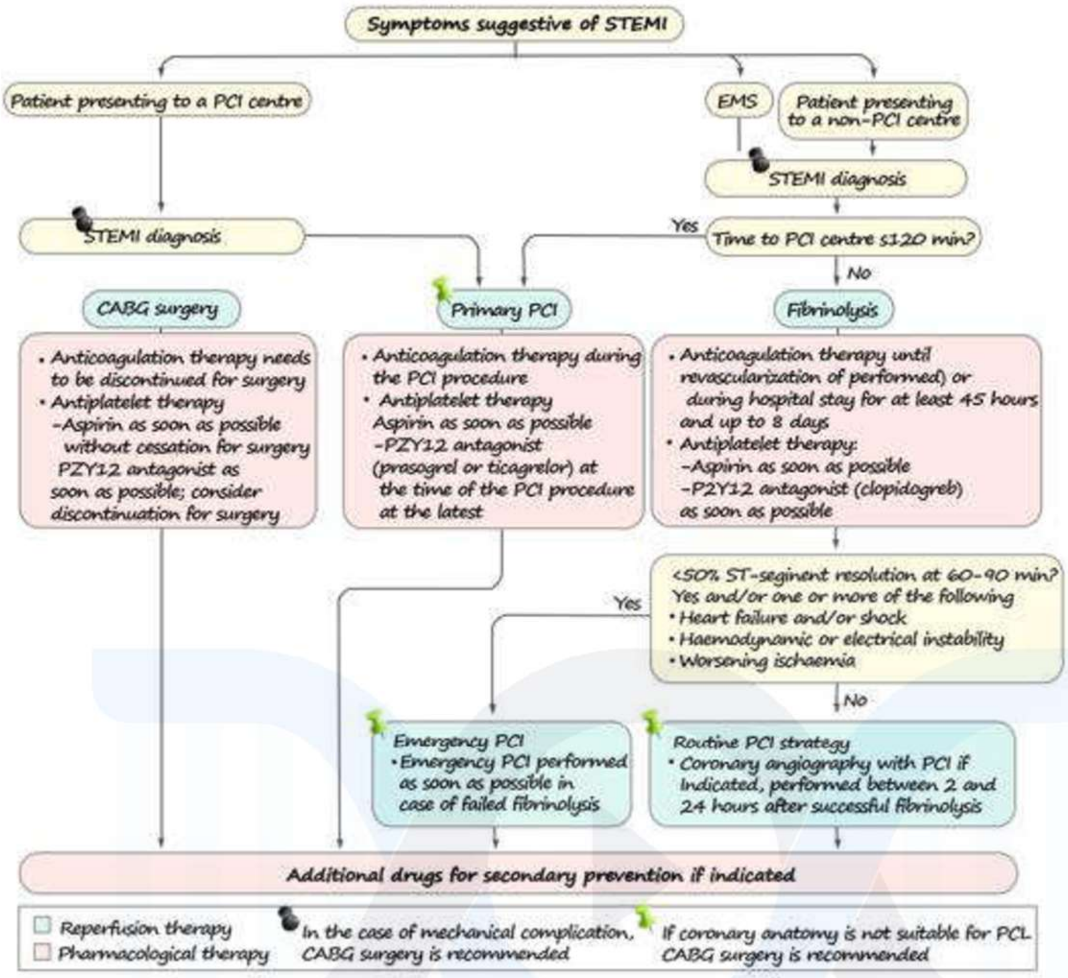
Refractory hypertension (SBP >180 mmHg and/or DBP >110 mmHg).
Advanced liver disease.
Infective endocarditis.
Active peptic ulcer.
Prolonged or traumatic resuscitation.

- Doses of antiplatelet and anticoagulant co-therapies in not repercussed patients

Doses of antiplatelet and parenteral anticoagulant therapies inpatients not receiving reperfusion therapy	
Antiplatelet therapies	
Aspirin	Loading dose of 150-300 mg orally followed by a maintenance dose of 75-100 mg/day.
Clopidogrel	Loading dose of 300 mg orally, followed by a maintenance dose of 75 mg/day orally.
Parenteral anticoagulant therapies	
UFH	Same dose as with fibrinolytic therapy.
Enoxaparin	Same dose as with fibrinolytic therapy.
Fondaparinux	Same dose as with fibrinolytic therapy.



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BASICS OF ELECTROCARDIOGRAPHY

Introduction 00:01:49

- Electrocardiogram – Graphic representation of electrical activity of heart
- Electrocardiograph – Instrument or device used to obtain this graph

History 00:03:55

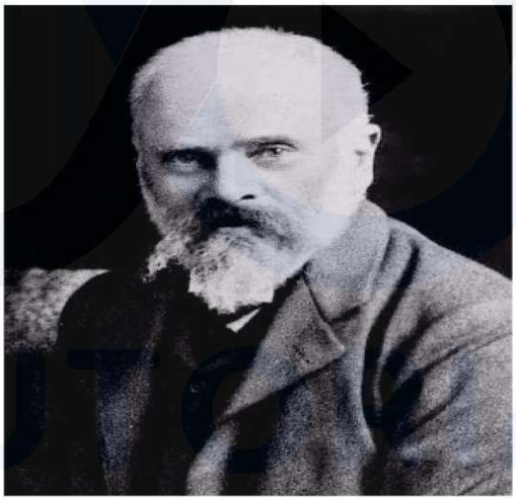

Fig: 1

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– Augustus Walter

↓

First recorded ECG in humans

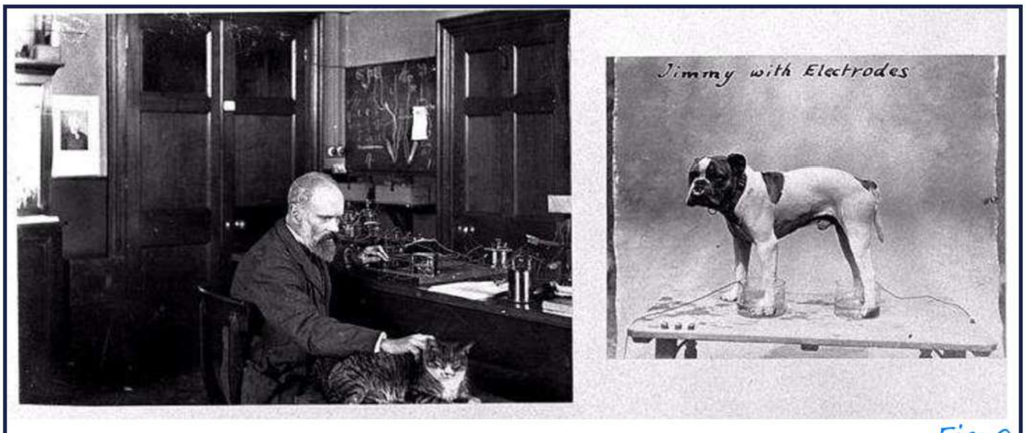

Fig: 2

Fig: 3

- William Einthoven

↓

- He began to use string galvanometer
- Was awarded the Nobel prize

Fig: 4

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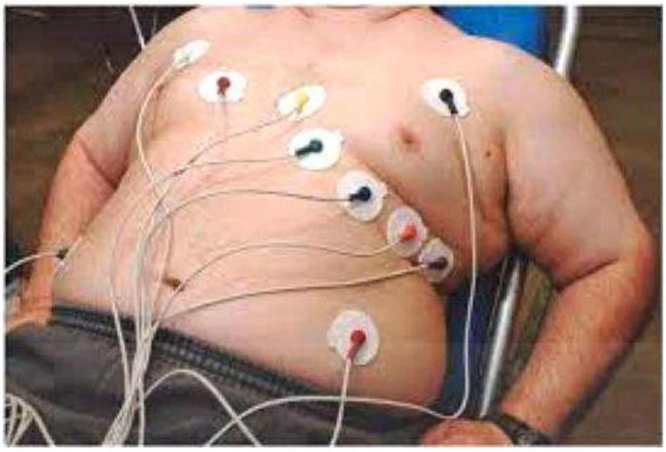

Fig: 5

Leads

Horizontal leads
↓
Horizontal plane
↓
Lead V1, V2, V3, V4, V5, V6

Frontal leads
↓
Frontal/Coronal plane
↓
Lead I Lead AVR
Lead II Lead AVL
Lead III – AVF

- Lead I,II,II,→ standard bipolar leads
- Lead aVR, aVL, aVF → unipolar limb leads

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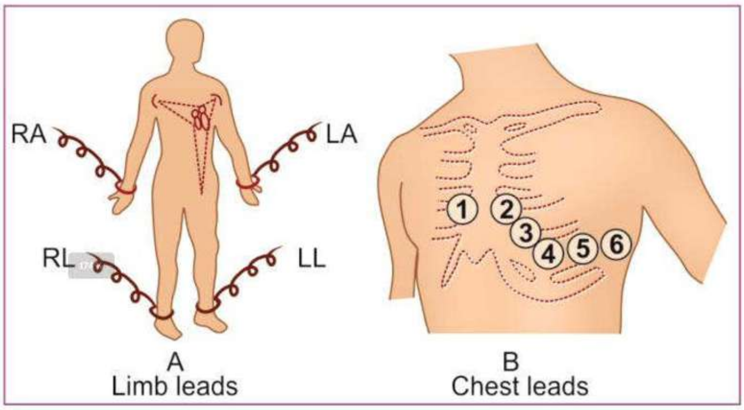

Fig: 6

- Electrodes are placed over R arm
  L arm
  L leg
- Ground electrode over R leg
- Connecting electrodes, we have leads

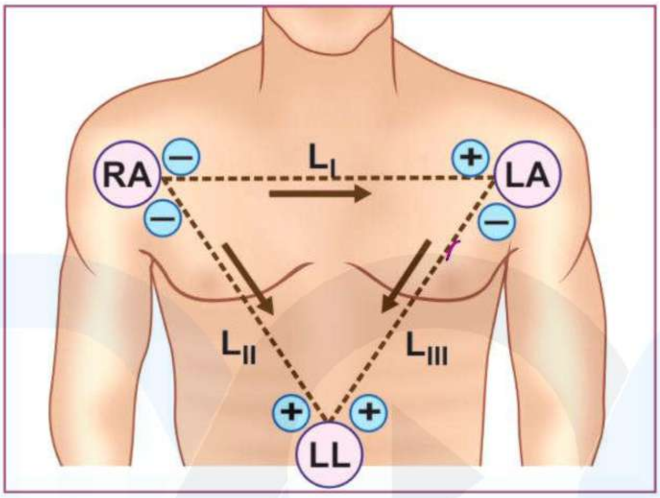

Fig: 7

- Bipolar lead: measures the potential difference between → 2 leads
- Beyond 15 cm, everything is equidistant
- Lead axis I → between R arm and L arm (lead I)
  Lead axis II → between R arm and L leg (lead II)
  Lead axis III → L arm and L leg (lead III)
- Lead axis of these 3 would from an equilateral triangle
  →Eithnoven triangle

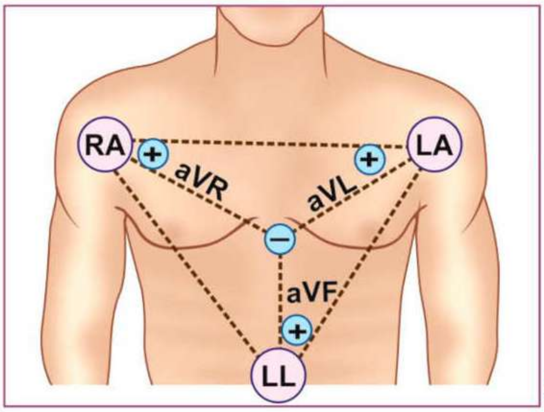

Fig: 8

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Augmented Leads

- Unipolar limb leads
- Measure potential difference from a center point where there is zero potential
- Smaller potential and augmented leads
- aVR
  aVL
  aVF
- V= unipolar lead

Horizontal Leads

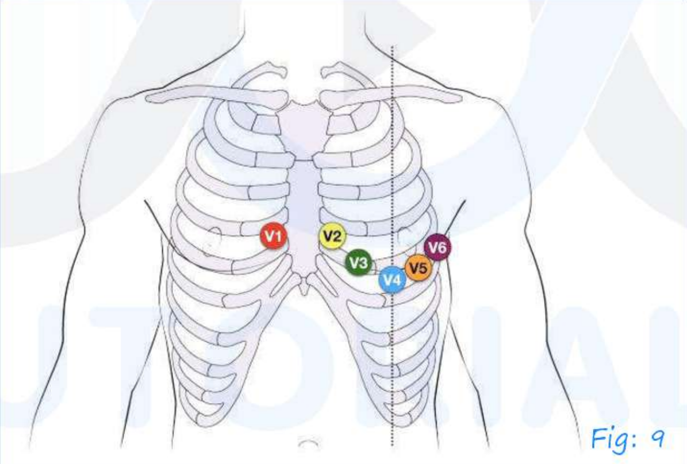

Fig: 9

LOGIN FOR SUCCESS

- V1 – R 4th ICS just adjacent to sternum
- V2 – l 4th IVS just adjacent to sternum
- V3 – Between V2 and V4
- V4 – L 5th ICs mid clavicular line
- V5 – Anterior axillary lone same level of V4
- V6 – Mid axillary line same level of V4

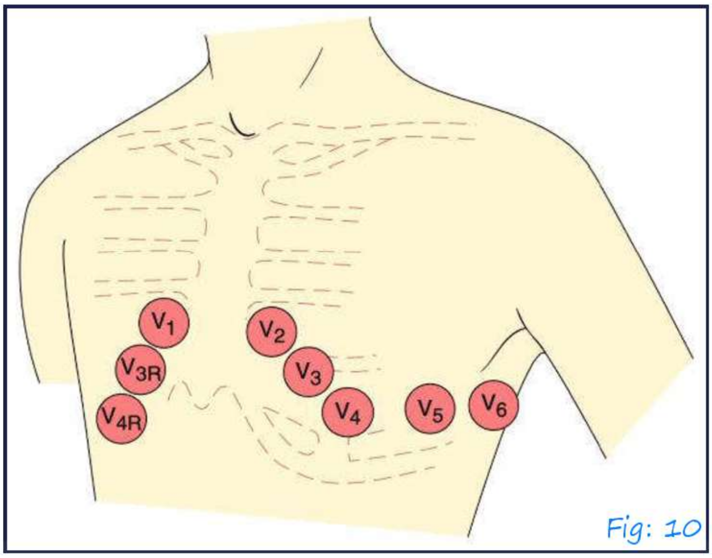

Fig: 10

- Additional electrodes are required in
  - RVMI → V3R, V4R

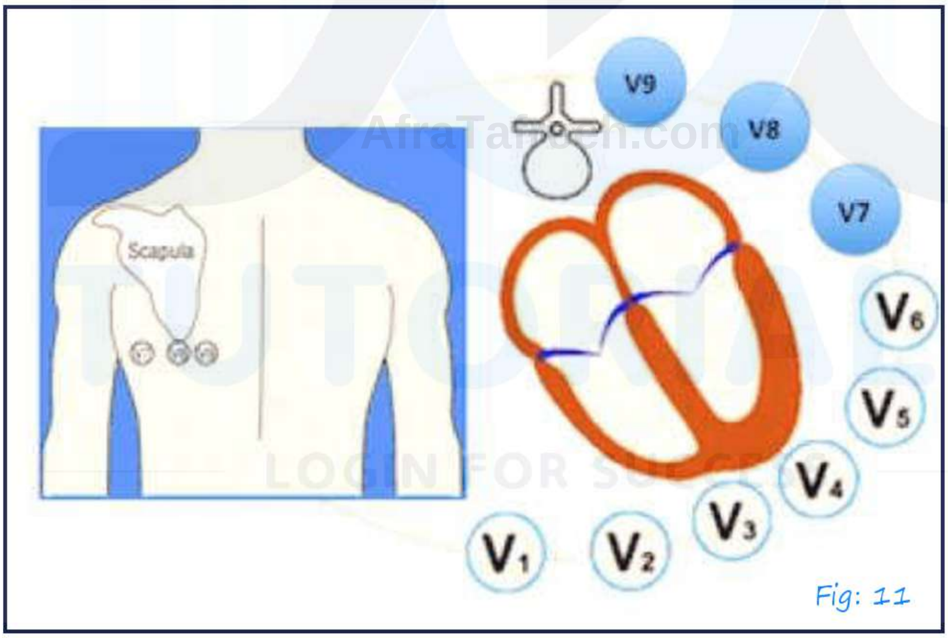

Fig: 11

- Similarly, additional electrodes v7, V8, V9 → posterior Wall Mi

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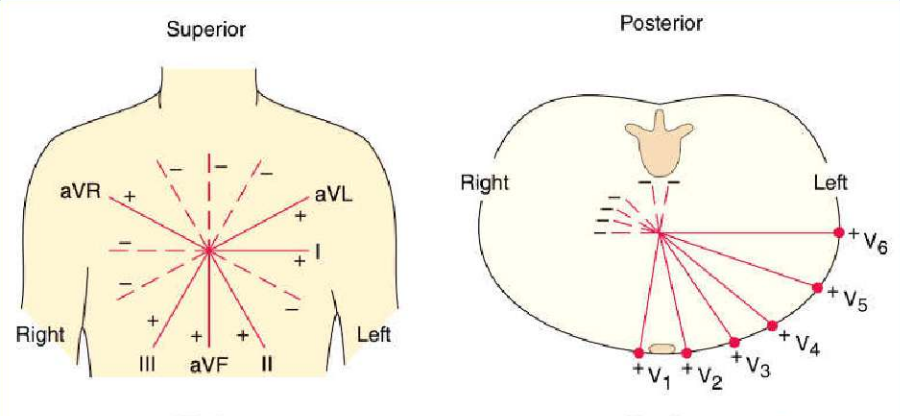

Fig: 12

- Lead I, II, aVF → contiguous leads

↓

Interior orientation

Conduction System of Heart 00:28:18

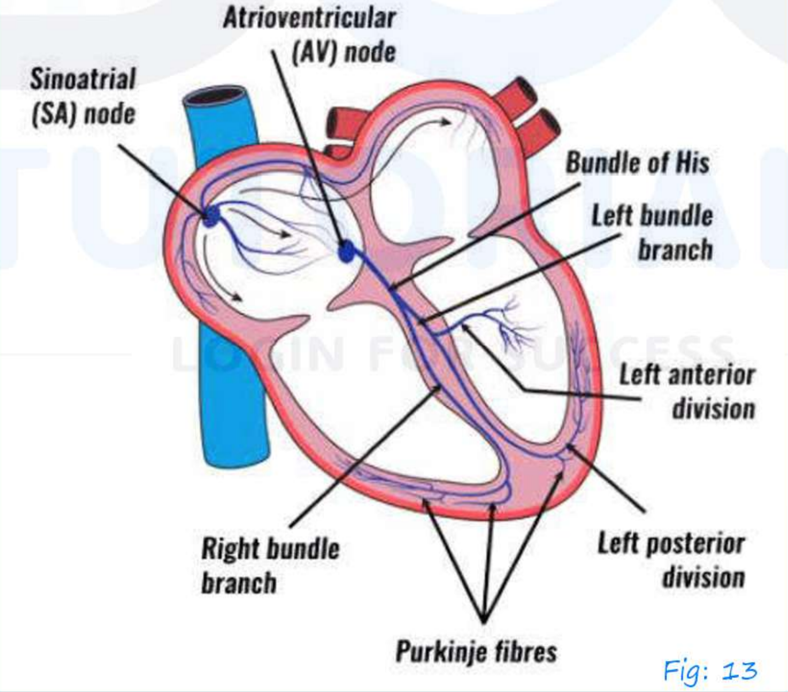

Fig: 13

- Pacemaker of heart – SA node
- From SA node, impulse travel to AV node
- In-between, there are internodal pathways connecting SA node and AV node

- Then impulse go to the bundle of his

R bundle branch | L bundle branch
↓
Supplies interventricular Septum also and subsequently divides
Into small anterior division
and
larger posterior division
And final ramification are the Purkinje fibers
↓
Fastest conducting

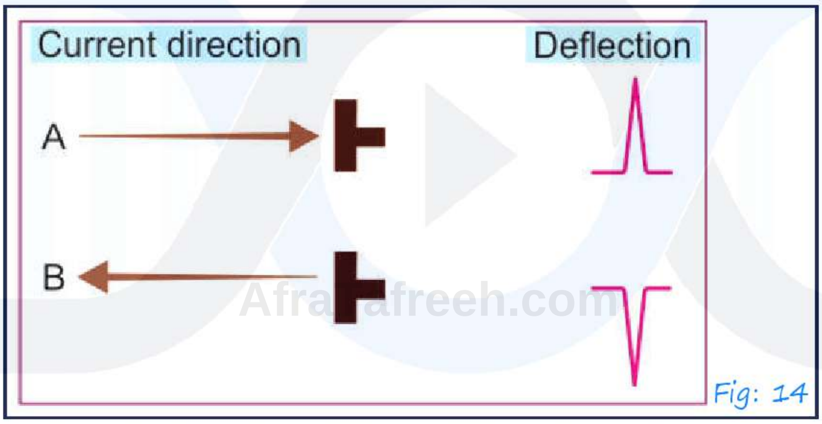

Fig: 14

General Principle

- Current moving towards positive electrode would Produce positive defection
- Current moving away would produce negative defection

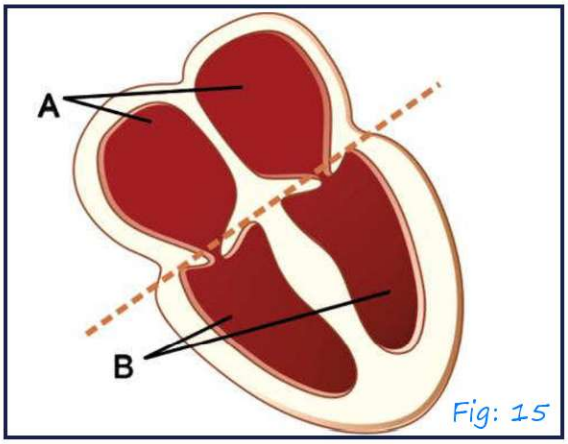

Fig: 15

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- If you compare chest wall of thin individual and obese Individual, amplitude of defection would be larger in thin individual

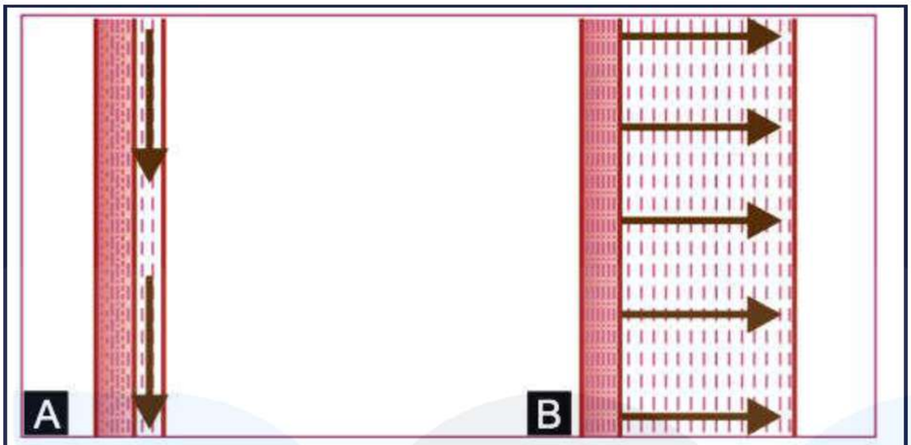

Fig: 16

A – Atrial activation → Longitudinal activation

B- Ventricular activation→ Transverse manner

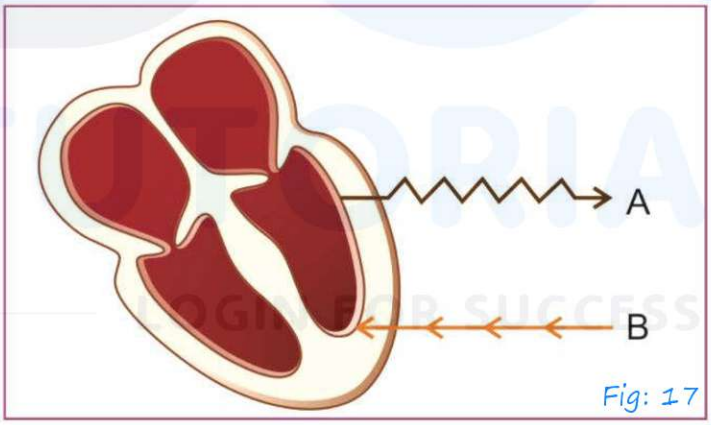

Fig: 17

- Depolarization moves from endocardium to epicardium
- Repolarization moves from epicardium to endocardium

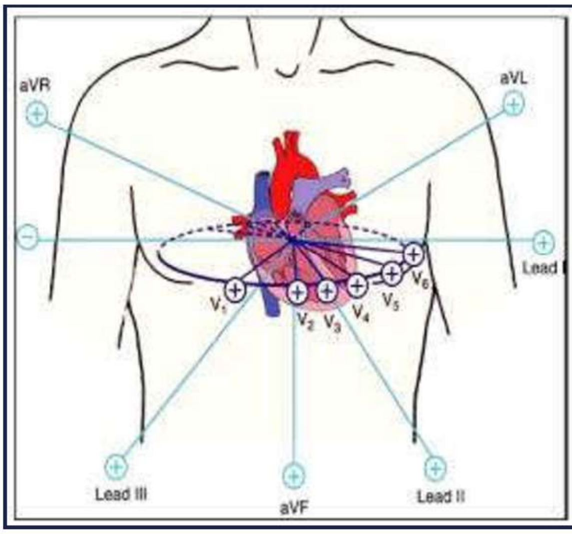

Fig: 18

- Vector of depolarization is almost same as lead axis of lead II
- Lead II is best for demonstration of p wave

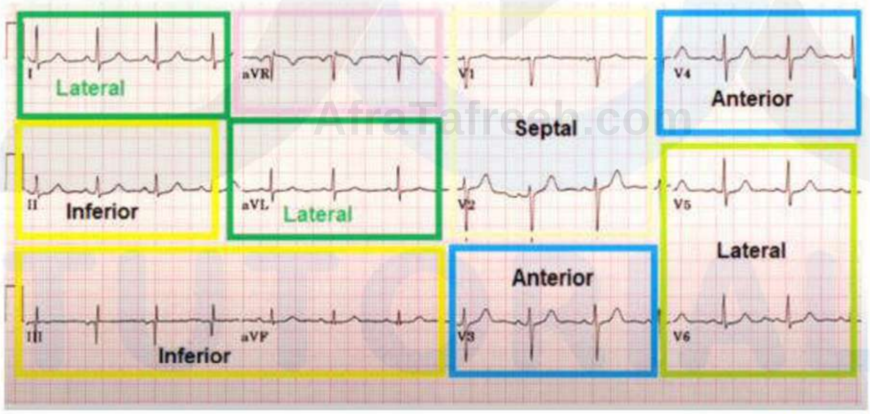

Fig: 19

- Lead I, aVL, V5, v6, Lateral leads
- Lead II, I, aVF → Interior leads
- Lead V1,V2, → septal leads
- Leads V3, V4 → Anterior leads

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ECG Paper 00:40:23

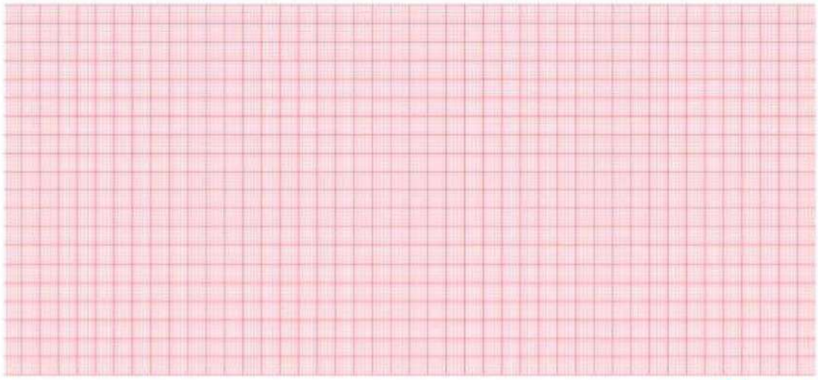

Fig: 20

- Thermosensitive paper
- Contains horizontal and vertical lines

↓

Grids → square shaped boxes

Fig: 21

- ECG paper is actually loaded onto ECG machine
- Paper speed: - 25 mm/second
- Heated stylus will cause waves on ECG paper
- Normally. The stylus decolorizes the paper

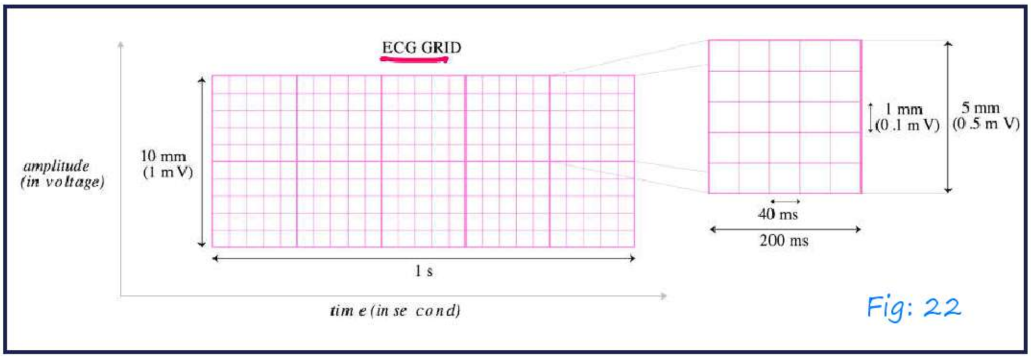

Fig: 22

- ECG paper consists of large squares
- Inside these squares → several small squares are present
- Time represented horizontally
- Amplitude represented vertically
- Width of small square horizontally or vertically is 1 mm
- 1 mm Horizontally + 40 milli seconds

  5 mm + 200 milli seconds
- Paper speed is such that it moves large 5 squares in one second
- To produce 1 mv signal → 10 mm vertically
- 1mm vertically = 0.1 mv

  5mm vertically = 0.5 mv

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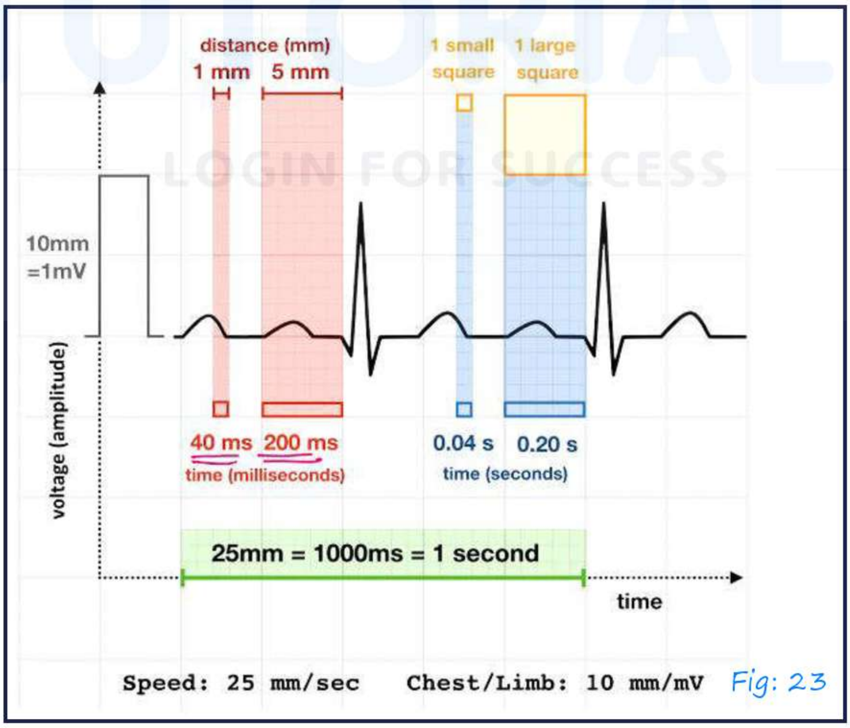

Fig: 23

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Electrical Events 00:49:22

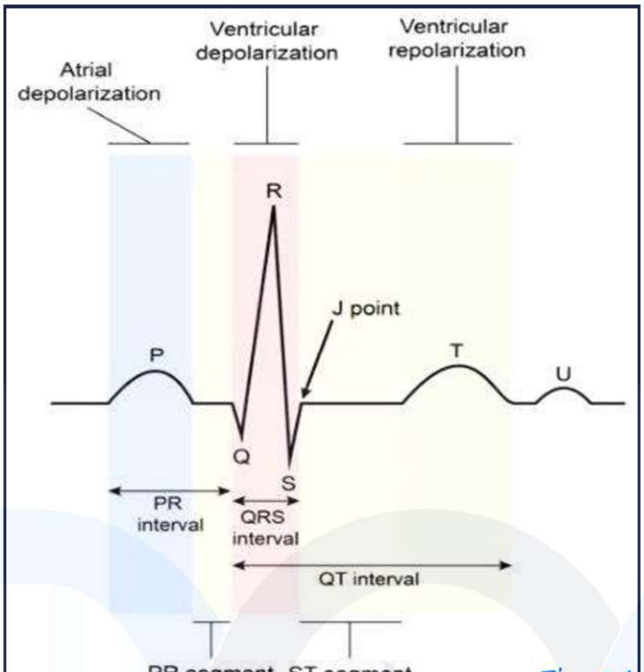

Fig: 24

- P wave – atrial depolarization
- Q wave – septal depolarization
- QRS complex – ventricular depolarization
- T wave – ventricular repolarization
- U wave – Delayed repolarization of papillary muscle
- Prominent u wave may be present in hypokalemia
- Atrial repolarization is hidden inside the ventricular Depolarization

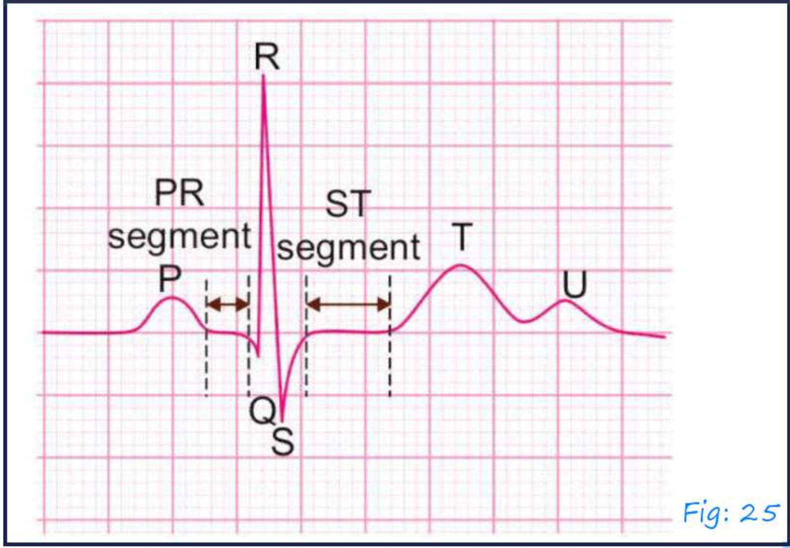

Fig: 25

- When you have segment → there is an isoelctric line
- PR segment → starts from end of P wave to the beginning of
  QRS complex
- ST segment → from end QRS (J point) to the beginning of T wave

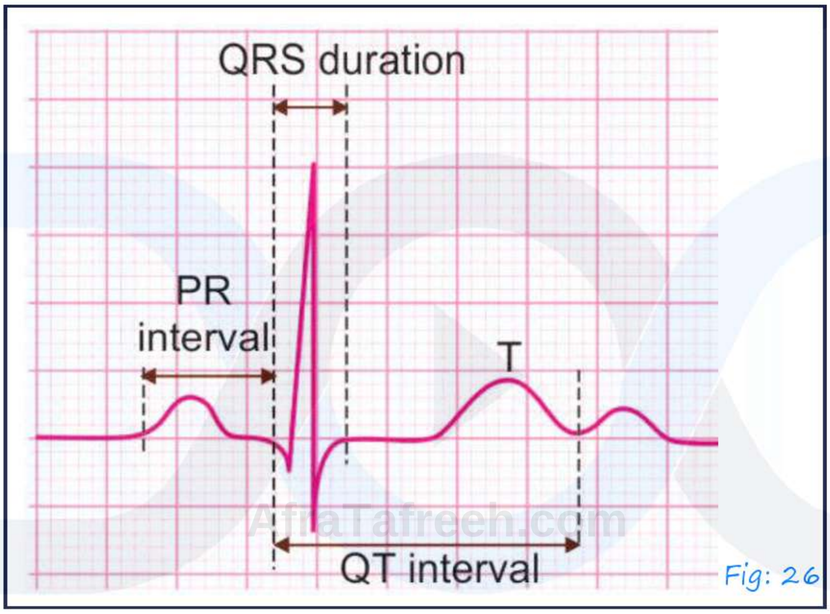

Fig: 26

- PR interval: - from beginning of P wave to beginning of QRs complex
- QT interval: - Beginning of QRS to end of T wave
- ST segment also forms an early part of repolarization

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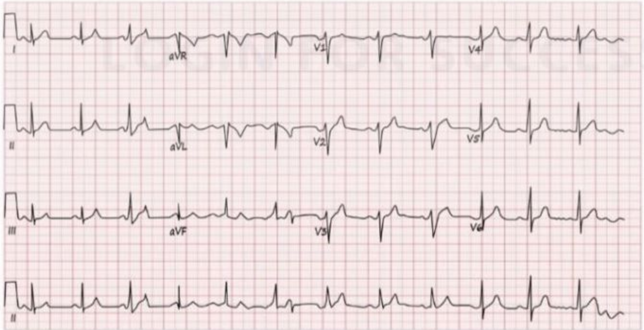
INTERPRETATIN OF ECG PART – I

Steps of ECG interpretation 00:02:25

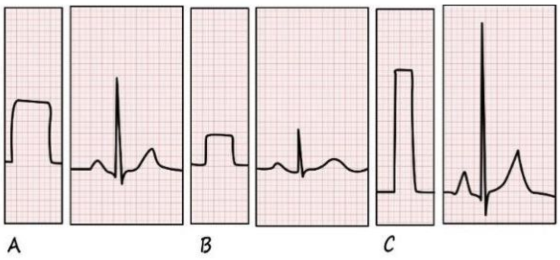
- Standardization
- Rate
- Rhythm
- Axis
- P wave
- PR interval
- QRS complex
- ST segment
- T wave
- QT interval
- Miscellaneous

Standardization 00:04:08



- Look at caliberation signal
- N scenarios: – 1 mv– 10 mm vertical deflection
- Normally the height of caliberation signal – 2 large boxes

- Normally the width of calibeartion sign – 1 large box



A-Normal standardization

B-Half standardization

C-Twice normal standardization

Assessment of Heart rate 00:07:18

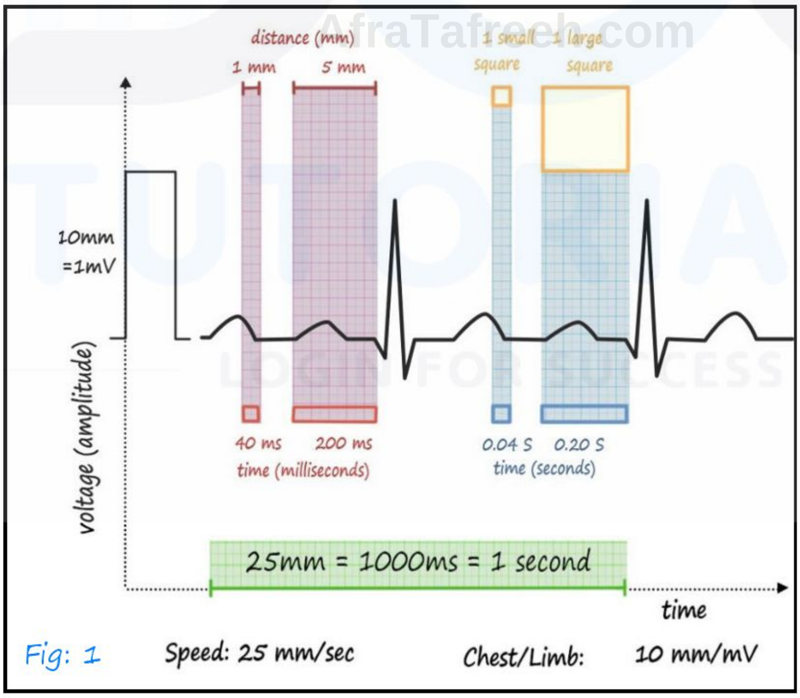


Fig: 1

- Conventional paper recording speed – 25 mm/sec
- 1 small square = 40 milli sec
- 1 large square = 200 milli sec

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- 5 large square = 1000 milli sec → 1 second
- 50 large square = 10 seconds
- 300 large square = 60 seconds/1 minute

  (1500 small squares)

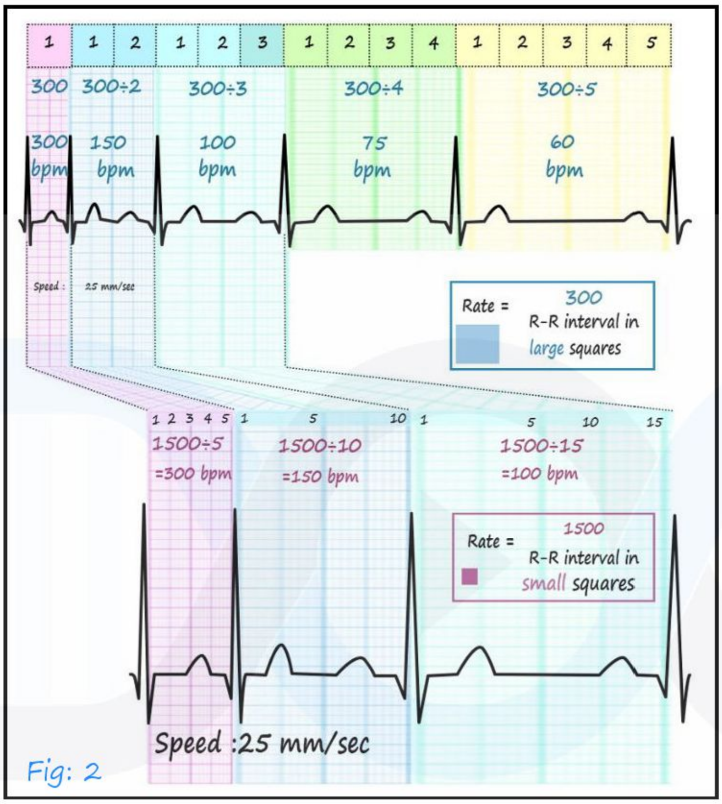


Fig: 2

$$\text{Rate} = \frac{300}{\text{Large squares in RR interval}}$$

$$\text{Rate} = \frac{1500}{\text{Small squares in RR interval}}$$

- Varying RR interval

  ↓

  Rhythm strip → how many R waves in the second

  Interval X 6

  ↓

  HR

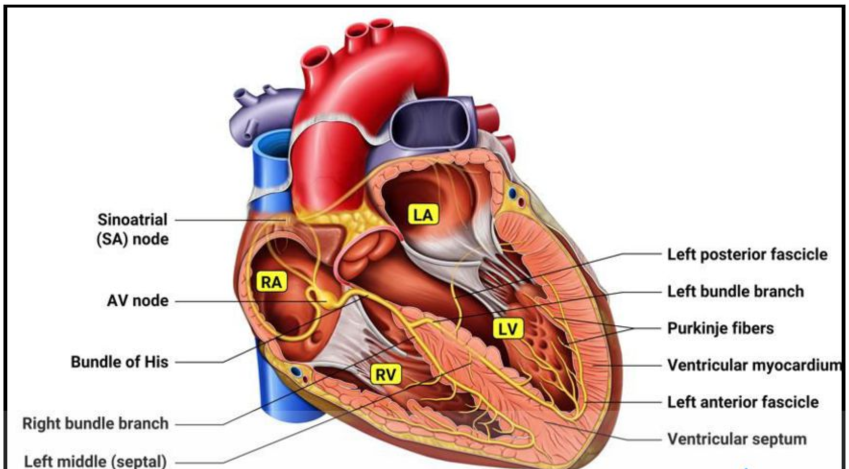
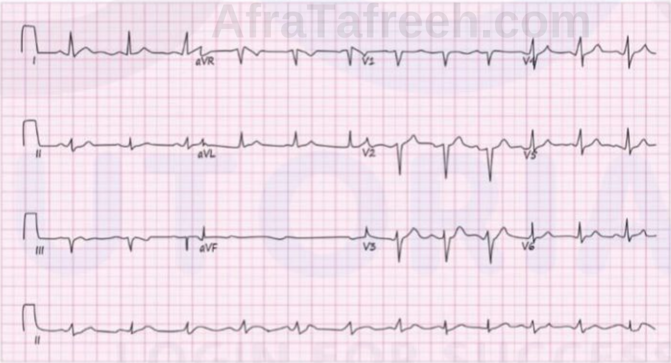


Fig: 3

- Pacemaker of heart determines the rhythm

↓

SA node (m/c)



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- Long strip of lead II is used for rhythm analysis

a. Sinus rhythm

- SA node is acting as the pacemaker
- Each P wave will be followed by normal QRS

A- Normal sinus rhythm: - 60 - 100/min

B- Sinus bradycardia: 60/min

C- Sinus tachycardia: > 100 /min

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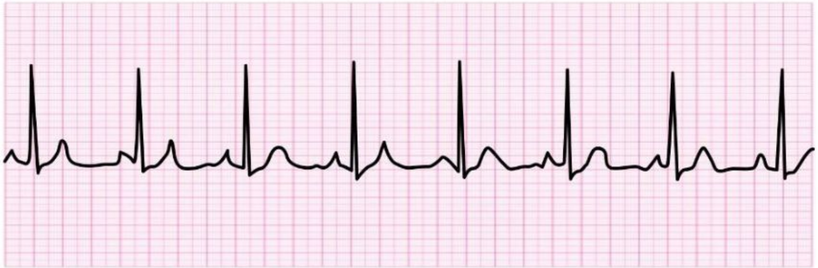
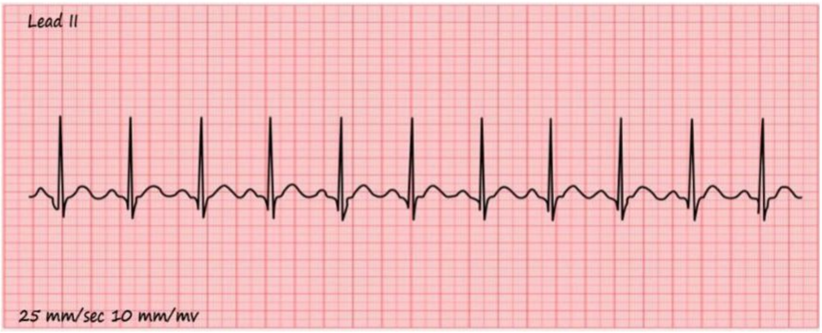


Normal sinus rhythm

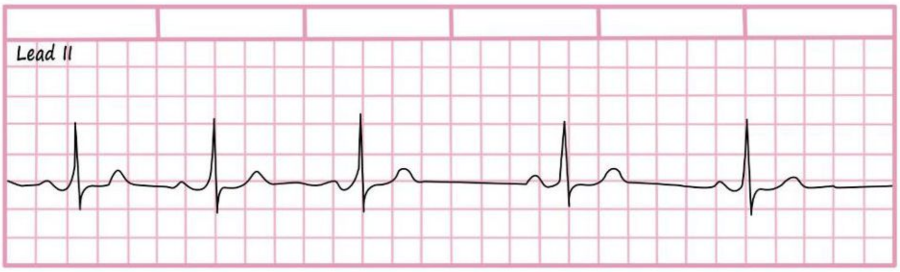
Normal Sinus Rhythm – ECG

- Regular rhythm at a rate of 60 – 100 bpm
- Each QRS complex is preceded by a normal P wave
- Normal P wave axis: P wave upright in leads I and II, inverted in a VR
- The PR interval remains constant
- QRS complexes < 100 ms wide
  (Unless co-existent interventricular conduction delay present)

Sinus Bradycardia



Sinus Tachycardia



Sinus Arrhythmia

- During inspiration- inhibition of vagus – increase HR
- During expiration – stimulation of vagus – decrease in HR

a. Junctional rhythm

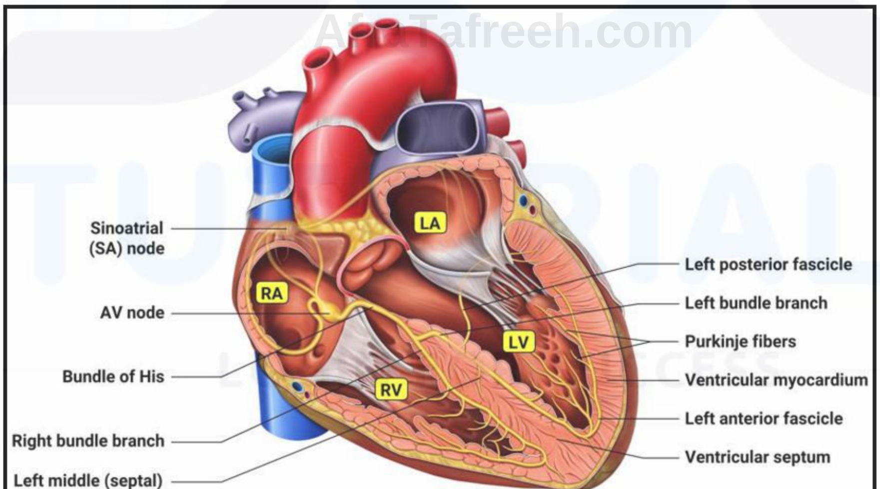


Fig: 4

- AV node is acting as pacemaker
- ECG: Either P is absent or inverted P waves

  A-Junctional escape rhythm: - 40-60/mm

  B-Accelerated junctional tachycardia: - 60-100/mm

  C-Junctional tachycardia: - > 100/mm

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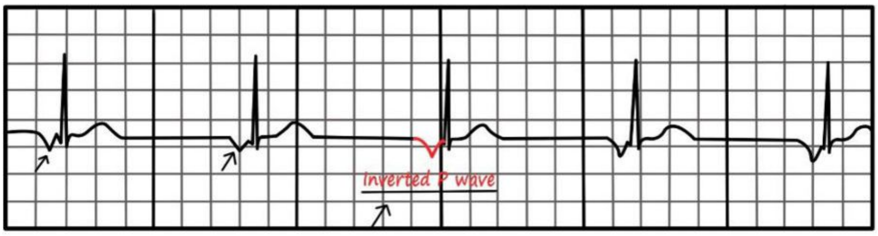
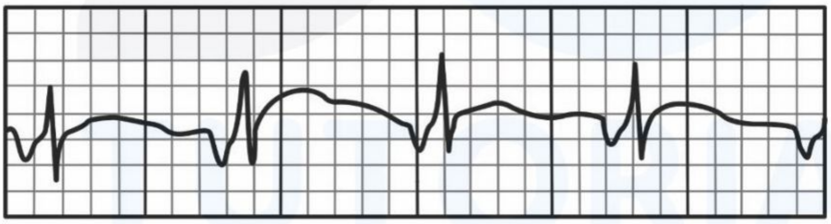
- Due to increased automaticity of AV node



Junctional escape rhythm

Junctional Escape Rhythm – ECG

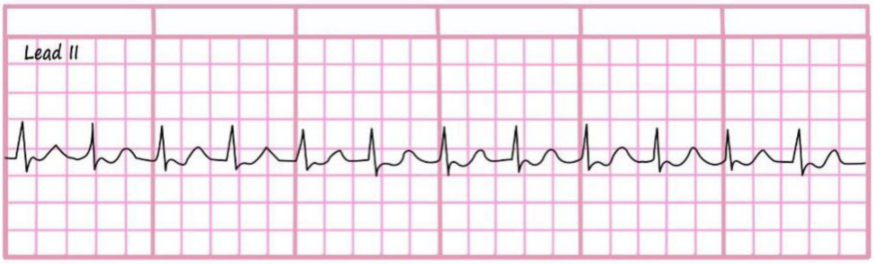
- Junctional rhythm with a rate of 40-60 bpm
- QRS complexes are typically narrow (<120 ms)
- No relationship between the QRS complexes and any preceding atrial activity (e.g. P-wave, flutter waves, fibrillatory waves)



Accelerated Junctional Rhythm – ECG

- Narrow complex rhythm; QRS duration <120 ms (Unless pre-existing bundle branch block or rate-related aberrant conduction)
- Ventricular rate usually 60-100 bpm
- Retrograde P waves may be present and can appear before, during or after the QRS complex
- Retrograde P waves are usually inverted in the inferior leads (II, III, aVF), upright in a VR + V1

- AV dissociation may be present with the ventricular rate usually greater than the atrial rate



Junctional Tachycardia

b. Idioventricular rhythm

- Pacemaker is below bundle of his

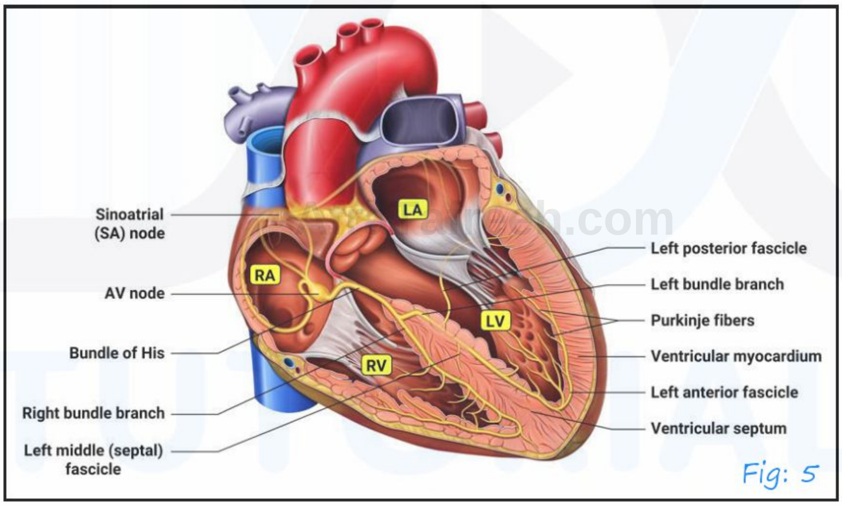


Fig: 5

- ECG: - wide QRS

  A-Idioventricular escape rhythm: - 40/min

  B-Accelerated idioventricular rhythm: - 40-100/min

  C-Idioventricular tachycardia: - > 100/min

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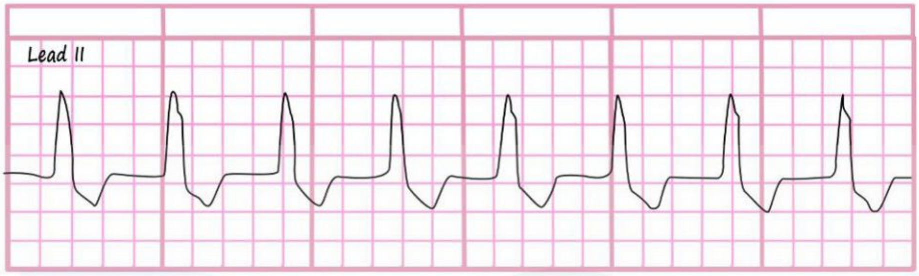
idioventricular escape rhythm



Accelerated idioventricular rhythm (AIVR)

↓

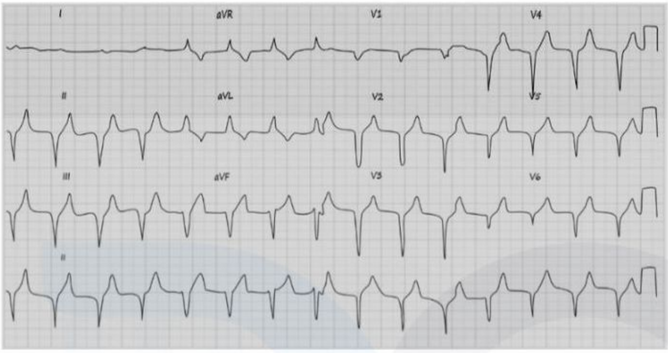
May be associated with capture beat

Fusion beats

AIVR Causes

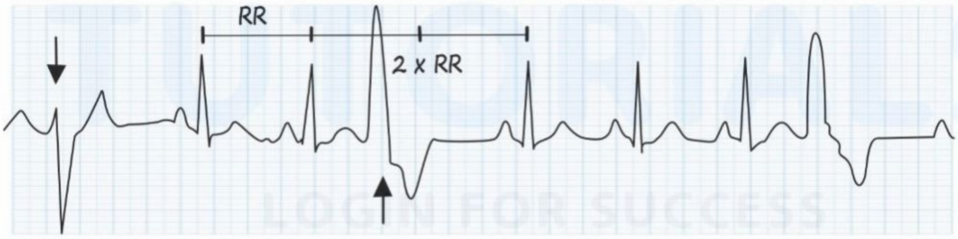
- Reperfusion phase of an acute myocardial infarction
- Beta-sympathomimetics such as isoprenaline or adrenaline
- Drug toxicity, especially digoxin, cocaine and volatile anaesthetics such as desflurane
- Electrolyte abnormalities

- Cardiomyopathy, congenital heart disease, myocarditis
- Return of spontaneous circulation (ROSC) following cardiac arrest
- Athletic heart



c. Geminey Rhythm

- Ventricular generation of ectopic impulse
- ECG: PVC (premature ventricular complex)



Multifocal PVC

↓

Compensatory pause followed by 2 NR

Geminey rhythm

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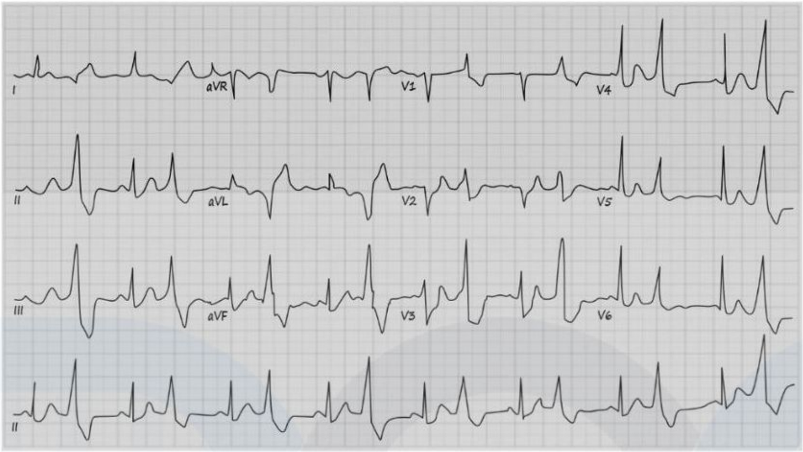
Inf every 2nd complex- PVC → ventricular bigeminy

- If every 3rd complex – PVC → ventricular trigeminey



Determination of Axis 00:51:58

- Synonyms of axis: - cardiac axis
  Electrical axis

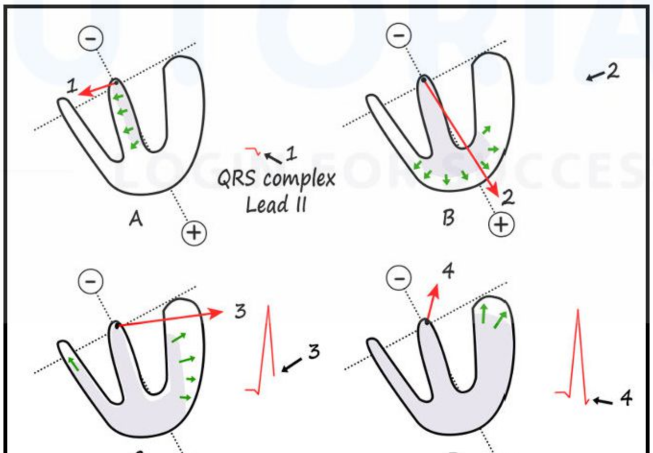


Fig: 6

- Step A- septal depolarization (L→R)
  B- Para septal depolarization
  C – Endocardial → epicardial

D – Base depolarized

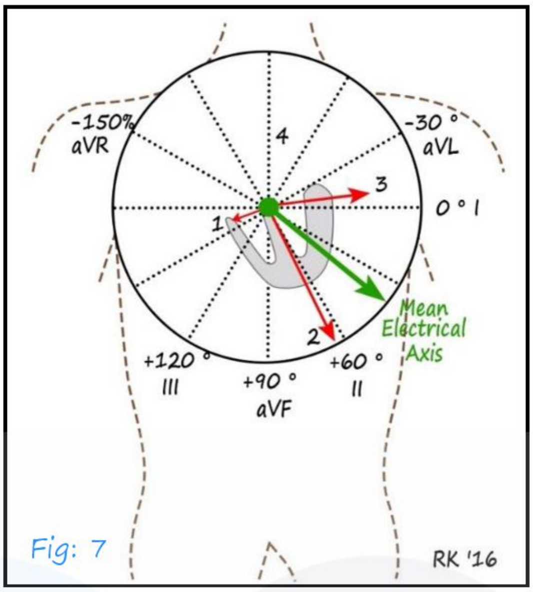


Fig: 7

- Cardiac axis – average direction of depolarization wave

-mean electrical axis

* Depolarization wave moves downwards and to left

[11 'O' clock → 5 'O' clock]

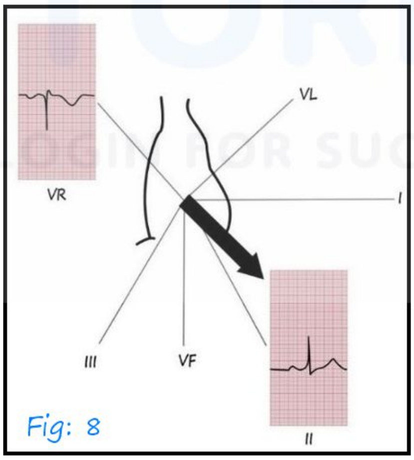


Fig: 8

- Mean electrical axis travels towards lead II

↓

+ve deflection

- Lead OVR will have negative deflection

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- Normal axis: - -30 to 90 o

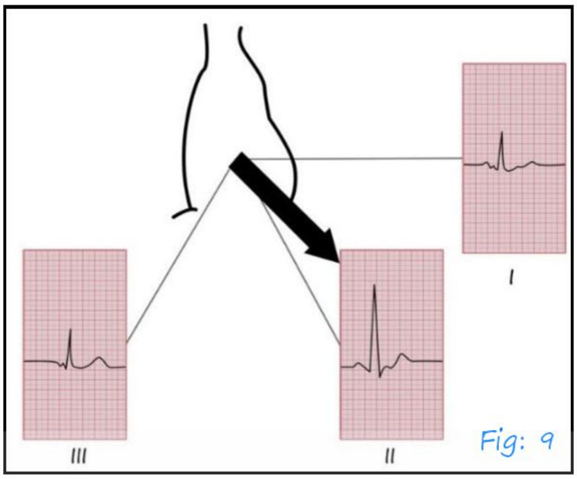

Fig: 9

- Lead II- +ve deflection
- Lead I& II - +ve deflection

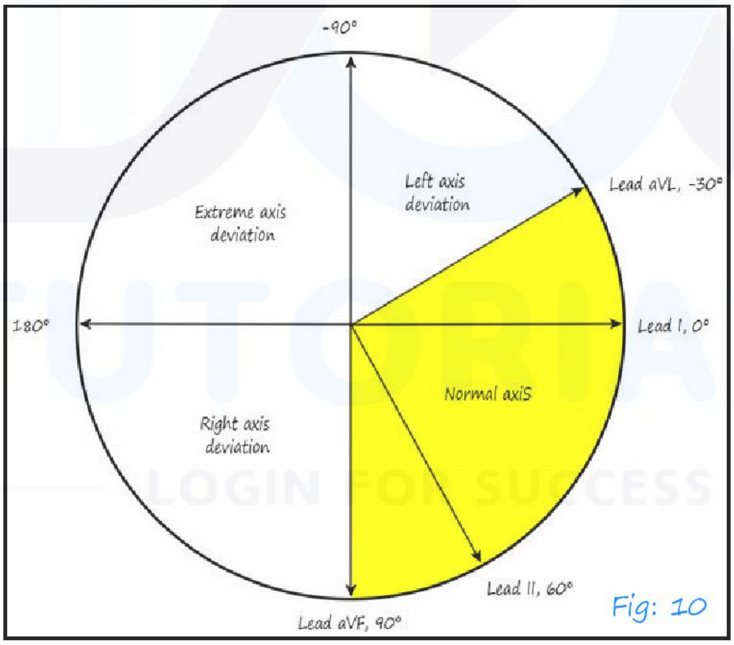

Fig: 10

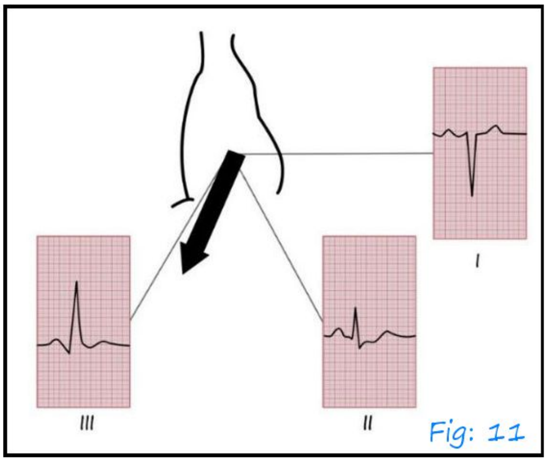

Fig: 11

- Patient with R ventricular hypertrophy

↓

R axis deviation

↓

Prominent positive deflection in lead II

Positive deflection in lead II

Negative deflection in lead I

Falls between +90 ° and 180°

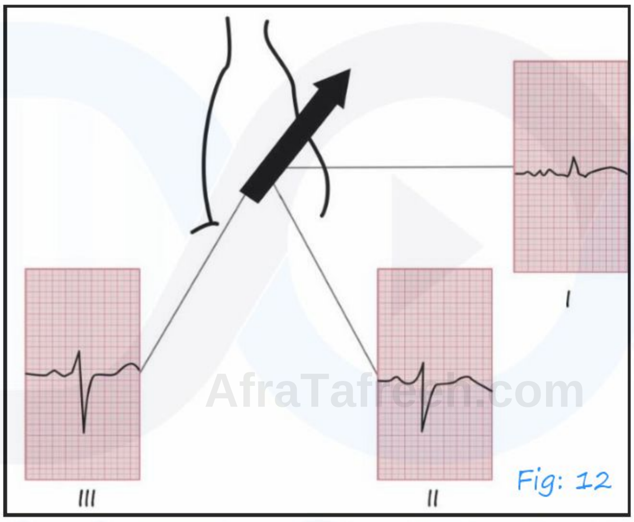

Fig: 12

- Patient has got left ventricular hypertrophy

↓

L axis deviation

+ve deflection in lead I

Predominantly -ve deflection in lead II and III

L axis deviation occurs due to conduction abnormalities

(- 30 to - 90°)

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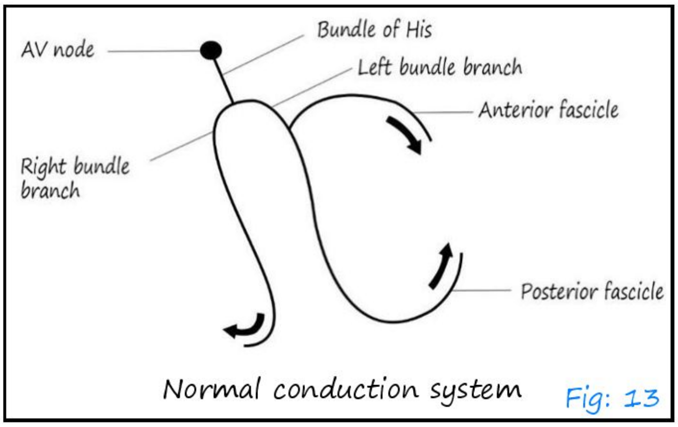


Normal conduction system Fig: 13

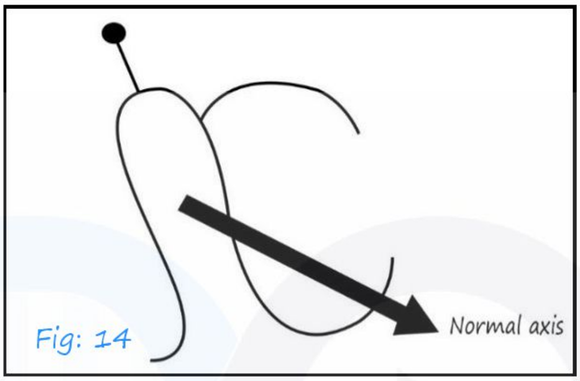


Fig: 14

Block in L anterior fascicle → L axis deviation

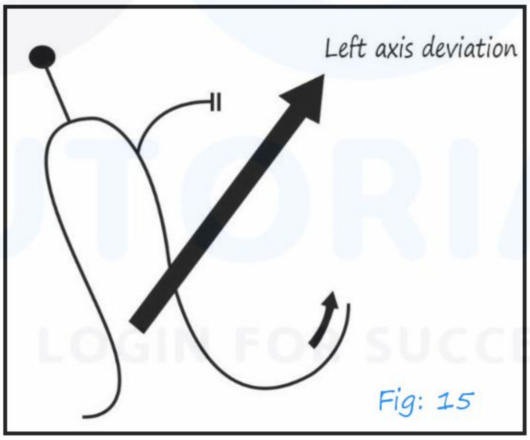


Fig: 15

Block in L posterior fascicle → R axis deviation

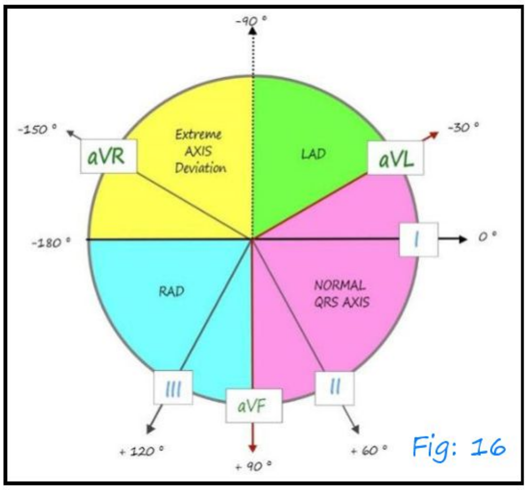
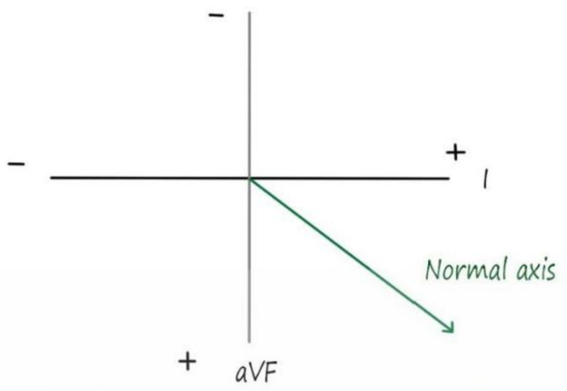


Fig: 16

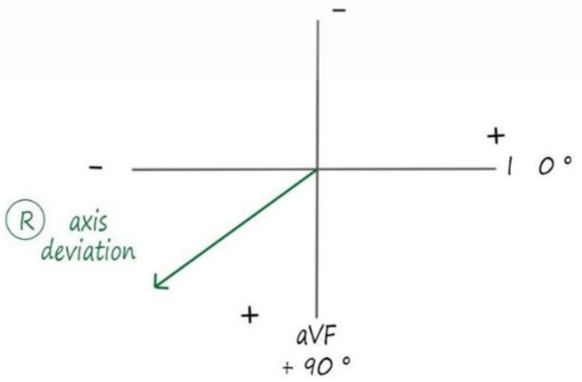
Determination of axis

- Quadrant method → lead I & aVF

0 0 & 90 0



- R-S in lead I- positive
- R-S in lead aVF – positive



- R-S in lead I - → - ve
- R – S in aVF → +ve

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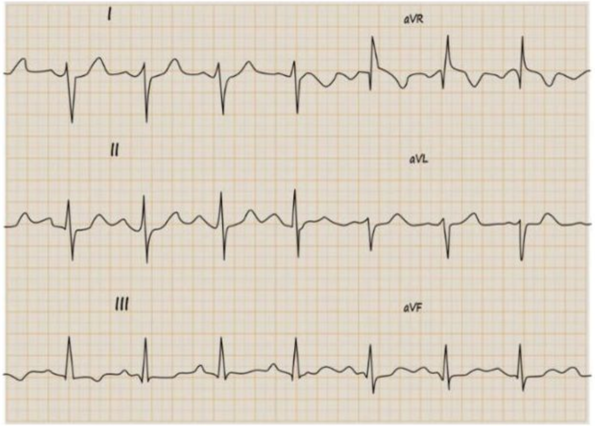

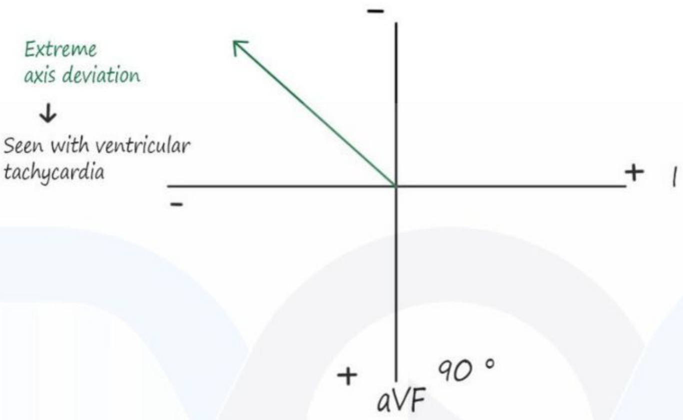

- R-S lead I & lead aVF – negative deflection

Analysis of P wave 01:17:58

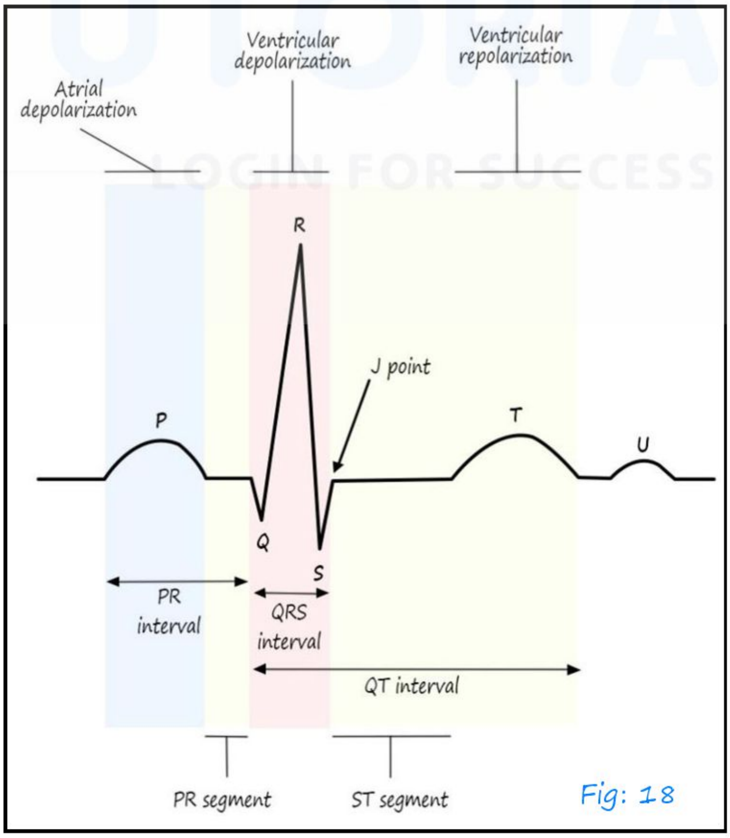

Fig: 18

- P wave – atrial depolarization

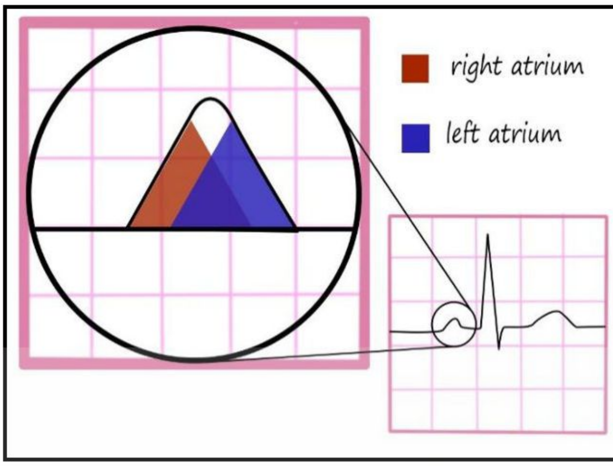

Fig: 19

Normal morphology of p wave

Ω – Smooth, dome, shaped

Duration < 120 ms

< 3 small < 120 ms

Amplitude < 2.5 mm

RAD Ω Ω LAD

R atrial depolarization followed by L atrial depolarization

- First 1/3rd of p wave → R depolarization
- Last 1/3rd of p wave → L atrial depolarization
- Middle 1/3rd do paw wave → RA+ LA

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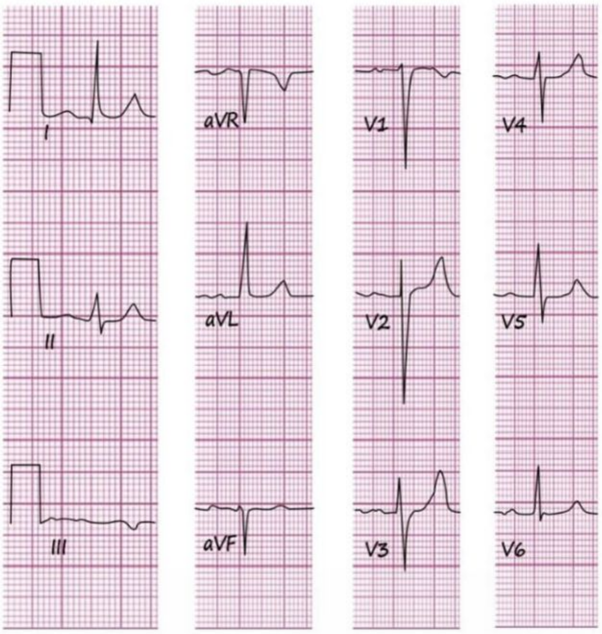
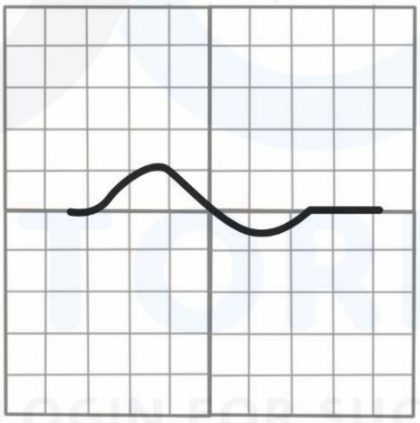


- In most of leads, p wave is a positive wave
- In lead aVR – negative p wave
- In lad v1 – biphasic cp wave



Analysis of p wave

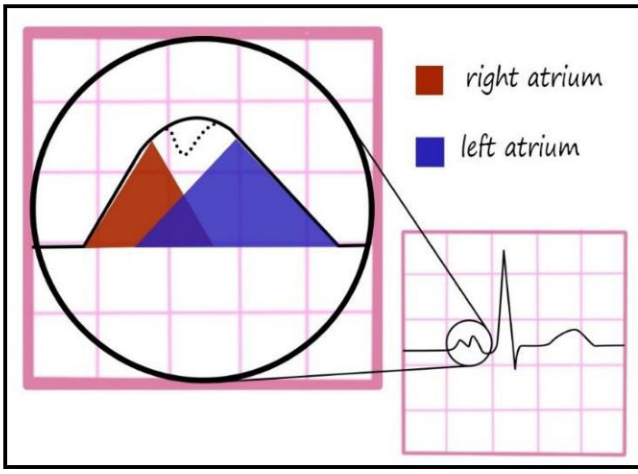


Fig: 20

- Best lead → II, lead v1
  - Is the wave present?
  - What is the morphology

Abnormal morphologies

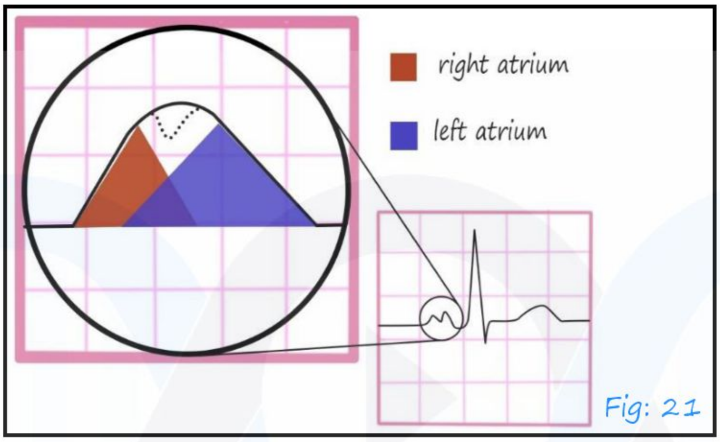


Fig: 21

- L atrial enlargement

Ω→ → duration > 120 mins

Nothing

↓

P mitral → L atrial enlargement

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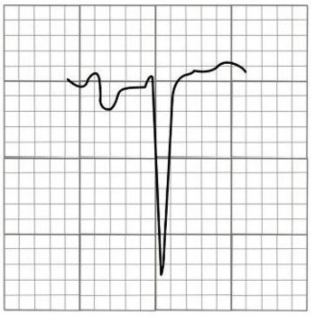

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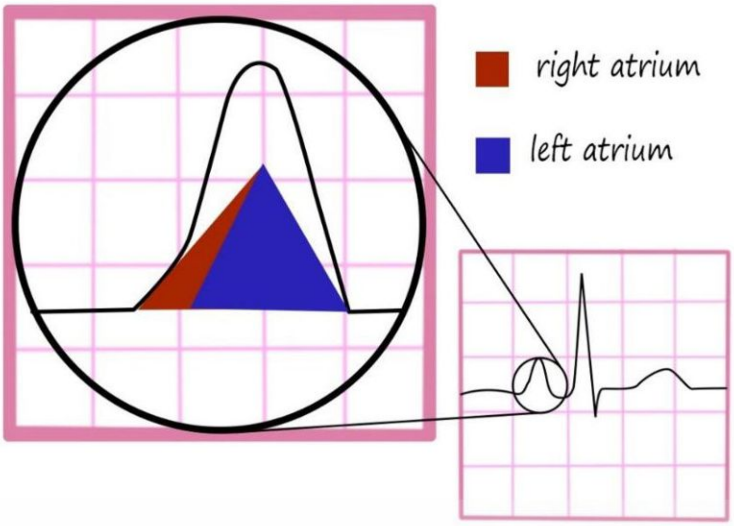


R atrial enlargement

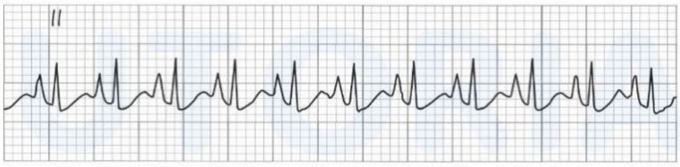
Fig: 22

Taller p waves

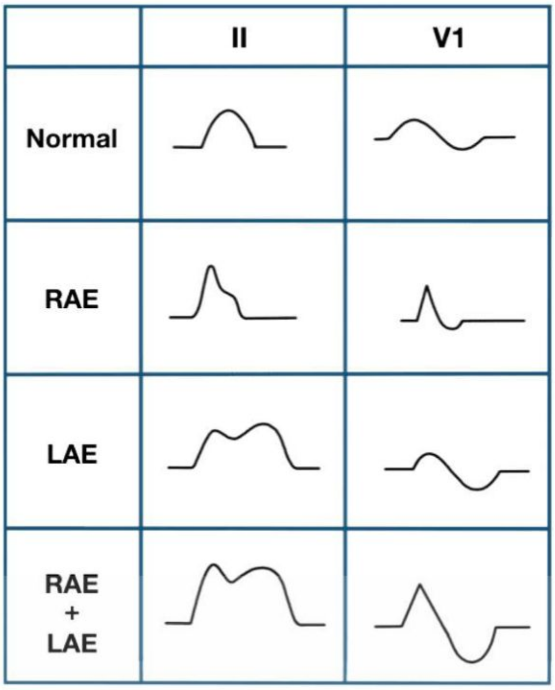
Amplitude increase

P- pulmonale

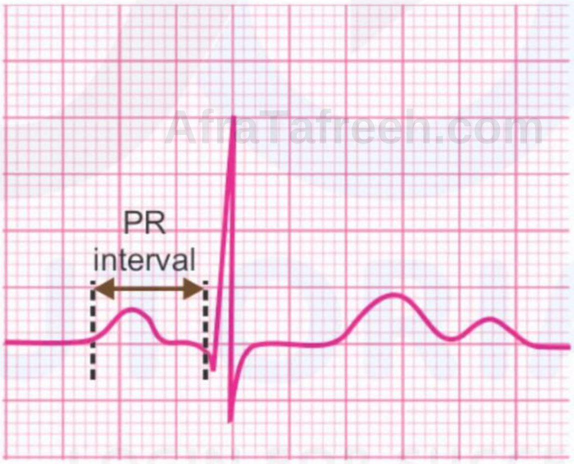
Pointed p waves



Amplitude > 2.5 mm



Analysis of PR interval 01:31:18



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- PR interval is from beginning of p wave till the beginning of QRS complex
- Normal duration of PR interval: - 120-200 ms (3.5 small squares)

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Significance

- Atrioventricular conduction time
- Time for atrial depolarization + AV nodal conduction delay + conduction across his bundle – purkinjee system

Abnormalities of PR interval

- Prolongation
- Shortening
- Varying PR interval

→ increase HR – PR interval shortens

Decrease – PR interval lengthening

PR prolongation

- Above 200 ms
- 1o degree heart block
- Drugs like Digoxin

B blockers
Verapamil
Diltiazem
} increase PR interval

Shortened PR interval

- Junctional rhythm → p waves inverted ↓ occur before, during or just after QRS complexes

- Pre excitation syndrome
  - Wolff Parkinson white syndrome
  - Lown ganong levine syndrome
- Atropine

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WPM syndrome

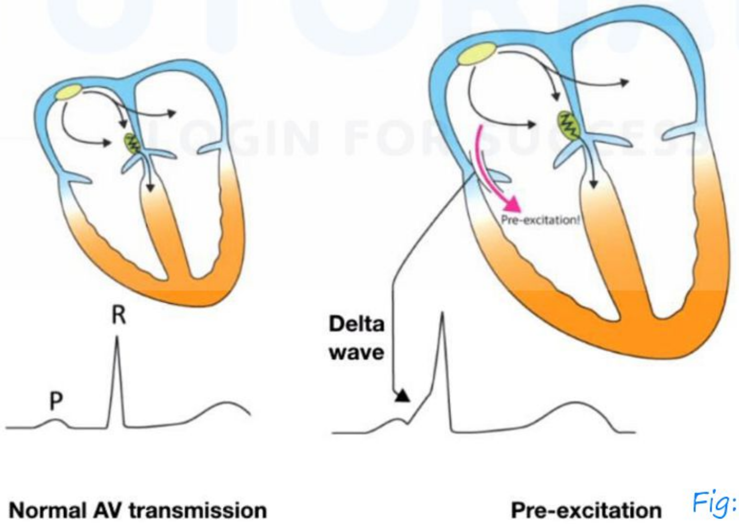

Fig: 23

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- Bypass tract called bundle of Kent

↓

If bypasses the AV node

- Pre – excitation

↓

Short PR interval

slurred upstroke of p wave

↓

Delta wave

- Wide QPS complex
- No Q waves

Lown Ganong levine syndrome (LGL syndrome)

- James's pathway – bypass tract
  - Bypass AV node – further propagation of his bundle purkinje system

ECG: - short PR interval

No delta waves

Q wave present

Normal duration of QRS

Condition with varying PR interval

second degree AV block, Mobitz type I

- Progressive prolongation of PR interval

  Subsequently missed beat

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- QRS complex → ventricular depolarization

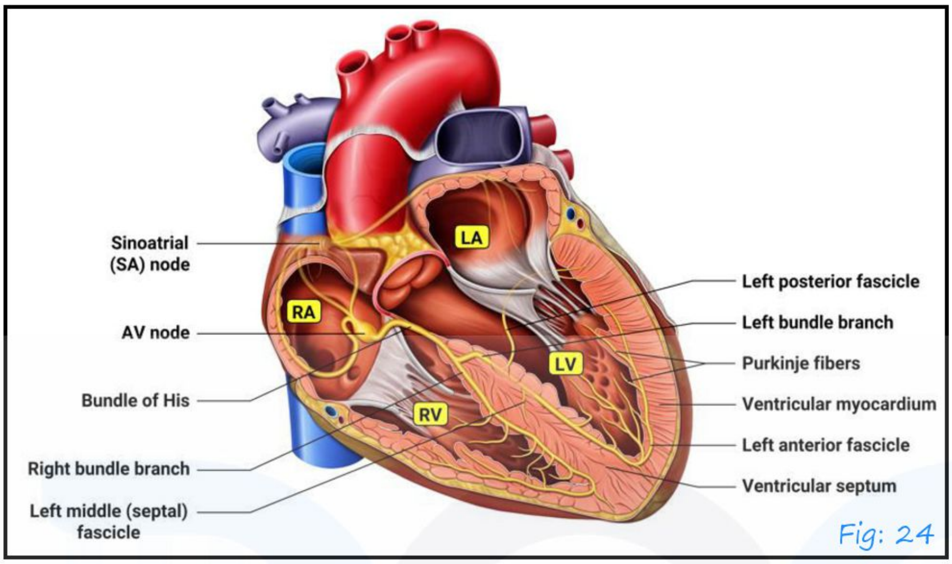

Fig: 24

- What is the relation of QRS complex to the p wave?
  - Is each P eave followed by QRS complex?
  - Is each QRS complex preceded by p wave?

2nd degree AV block (Mobitz type II)

VPC – ventricular premature contraction

- What is the morphology of the QRS complex?
  - Width
  - Shape
  - Height

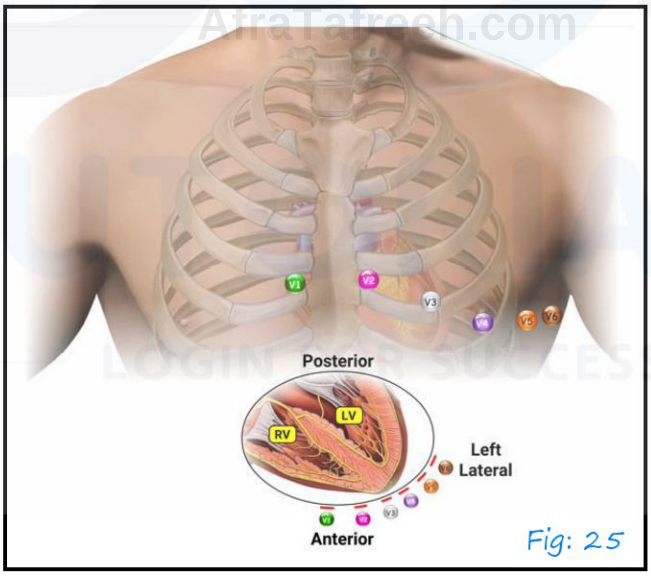

Fig: 25

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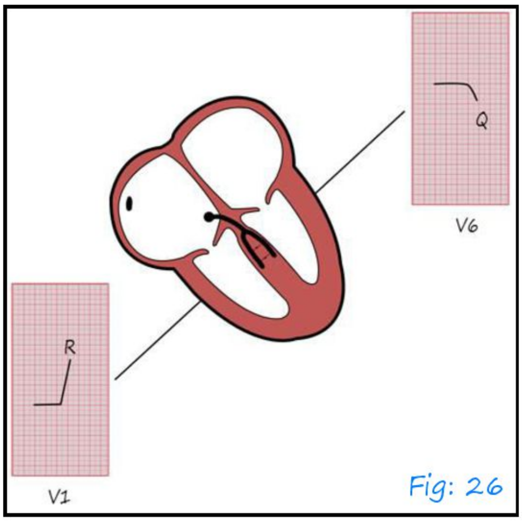


Fig: 26

i. Septal depolarization (L→ R)

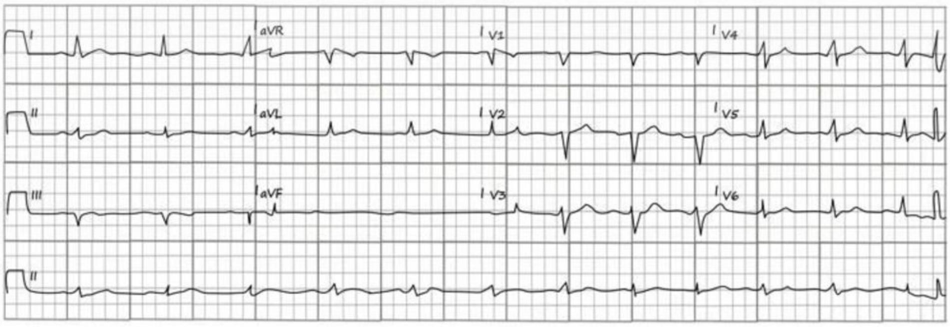
Direction of net vector is towards V1

Net vector is away from V^

Pathological Q wave

- > 40 milliseconds
- > 2 mm deep
- >25% of the height of the following QRS
- Present in lead V1-V3

- Associated with myocardial infraction



pathologic Q wave

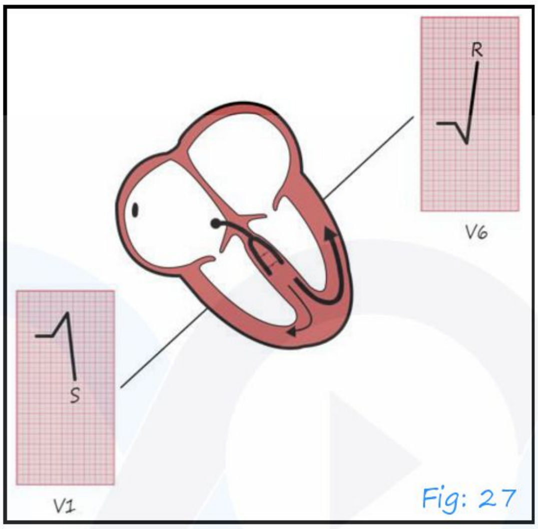


Fig: 27

ii. Ventricular depolarization

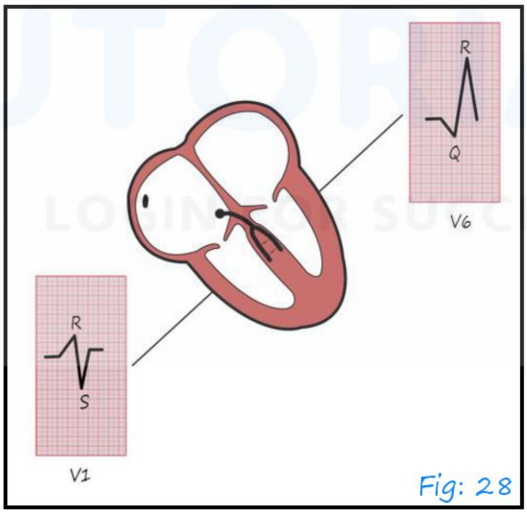


Fig: 28

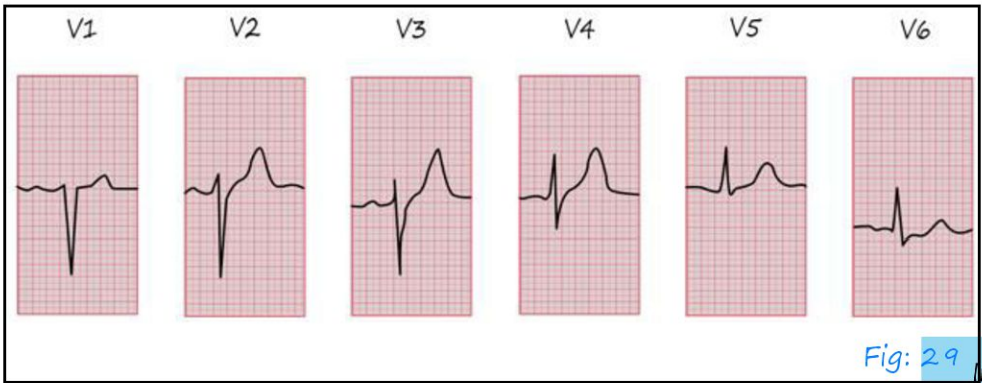


Fig: 29

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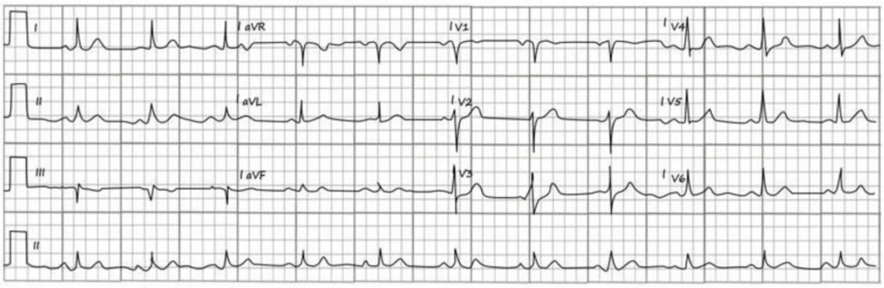
- Transition point: - Height of R > Depth of S

R wave progression



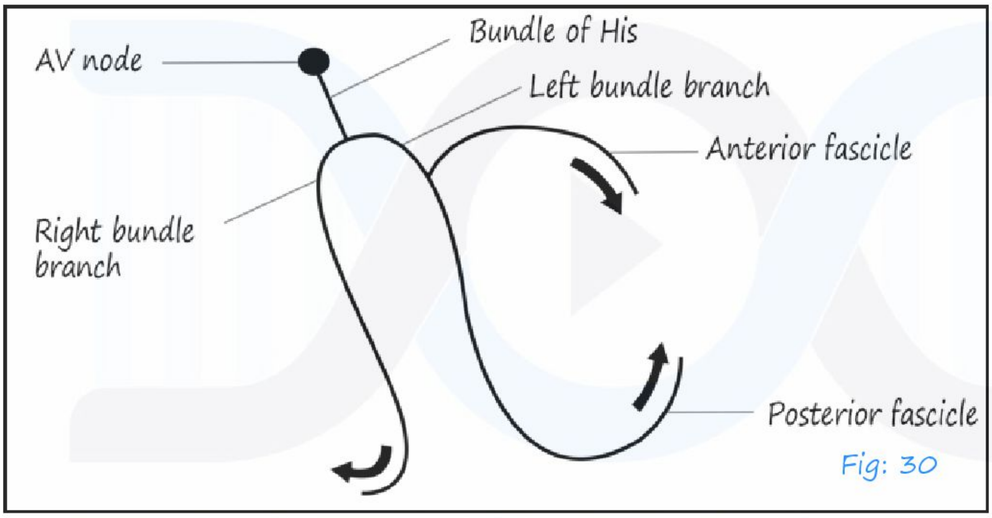
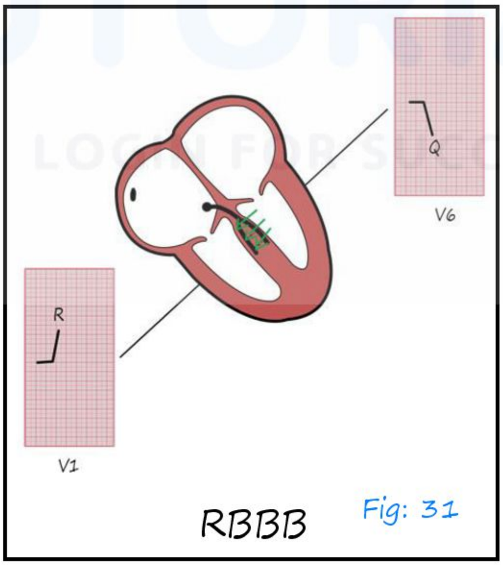
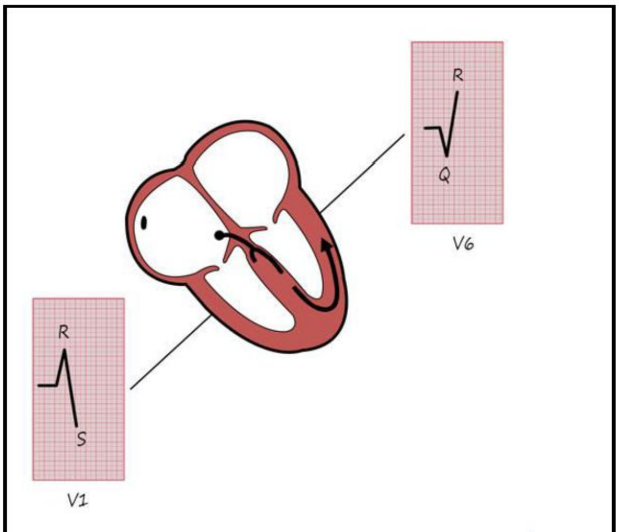


Fig: 30

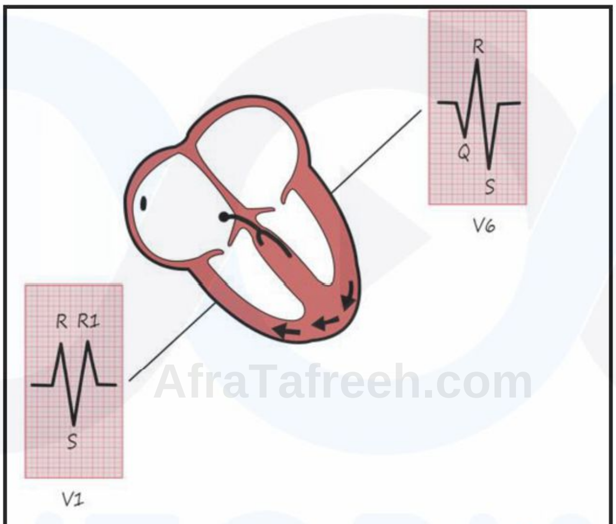


RBBB

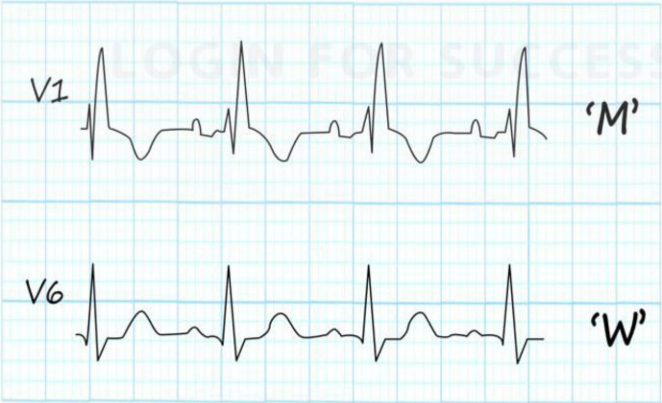
Fig: 31



Depolarization of ventricular mass Fig: 32



Depolarization of R ventricle Fig: 33



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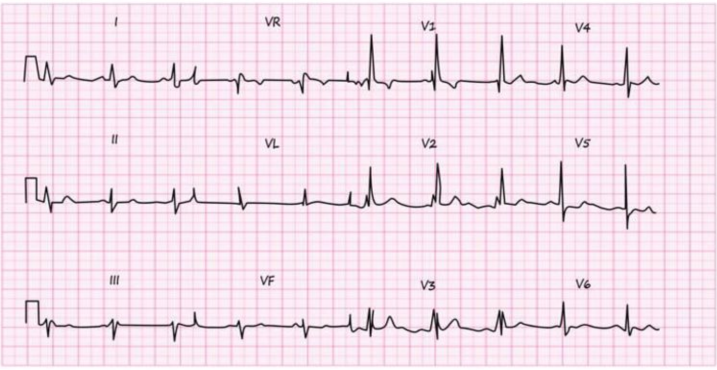

- N QRS: - < 120 ms

  (80- 100ms)

- RBBB > 1200 ms (> 3 small squares)

Causes of RBBB

- Physiological
- Right ventricular hypertrophy
- Pulmonary embolism
- Ischemic heart disease
- Myocarditis
- Cardiomyopathy

LBBB > 120 ms

LAHB ⎤
LPHB ⎦ duration 100- 120 ms

LAHB → L axis deviation

LPHB → R axis deviation

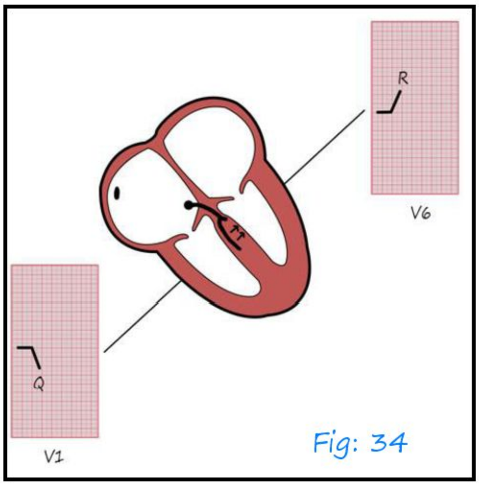

Fig: 34

- Septal depolarization via RBB
- -Ve deflection in V1

    positive deflection in V6

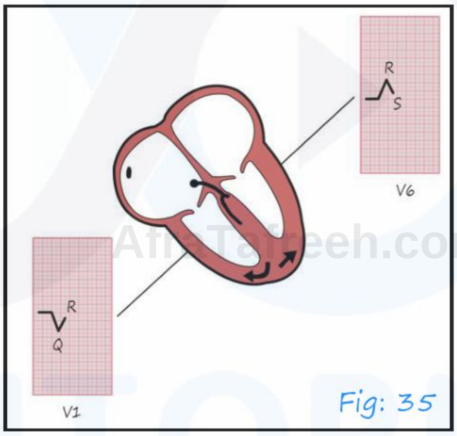

Fig: 35

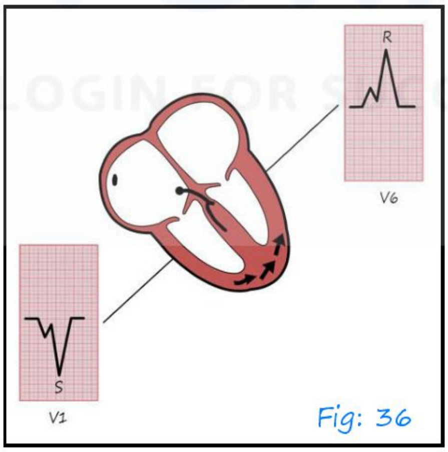

Fig: 36

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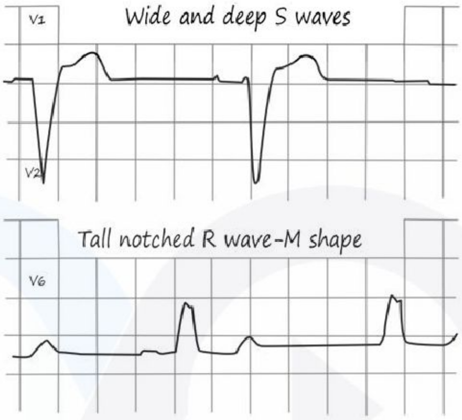

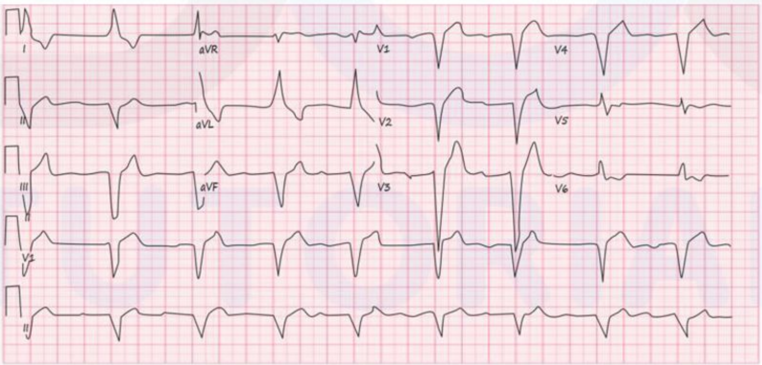

complete LBBB

Causes of LBBB

- Ischaemic heart disease
- Aortic stenosis
- Hypertension
- Dilated cardiomyopathy

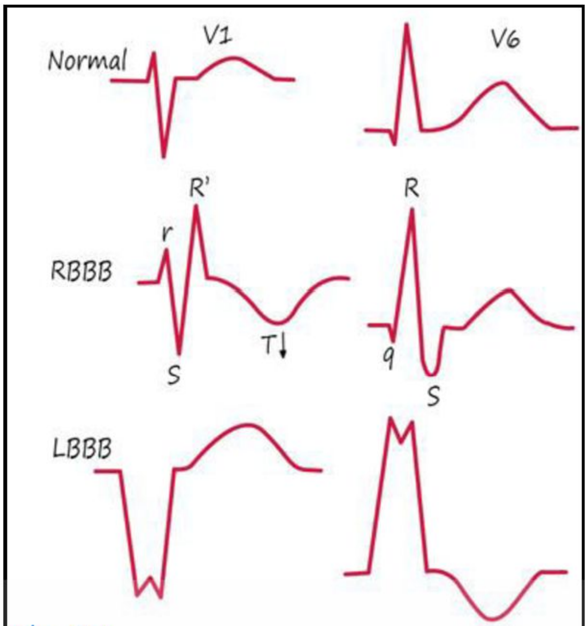

Fig: 37

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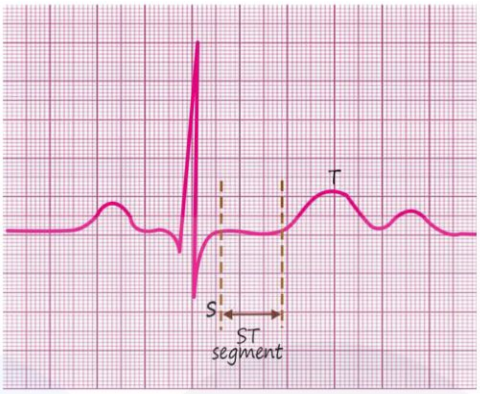
INTERPRETATIN OF ECG PART – II

Analysis of ST segment 00:00:21



- ST segment: – End of S wave to beginning go T wave

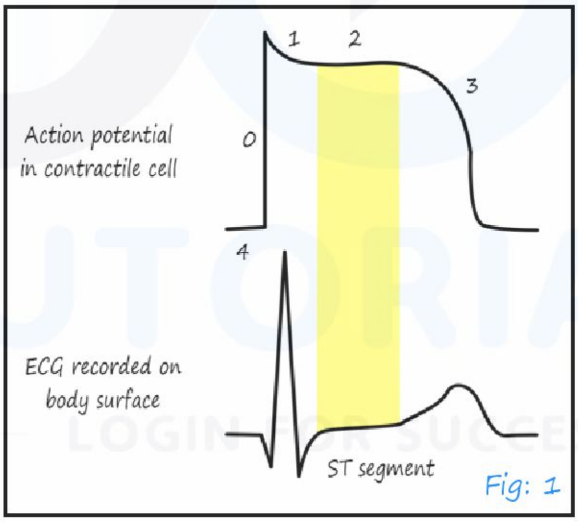


Fig: 1

- ST segment → Isoelectric segment
  → Part of ventricular repolarization

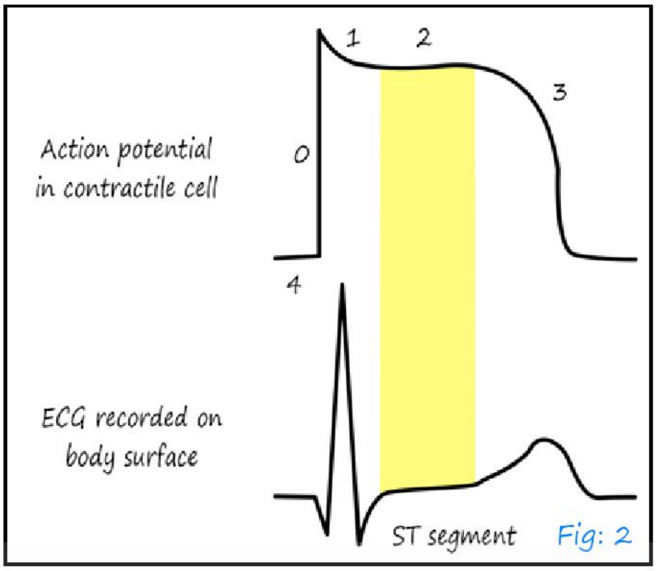


Fig: 2

- ST segment → corresponds to plateau phase of action potential
  - Extends from J point to onset of T wave
  - Corresponds to plateau phase of action potential
  - Membrane potential is relatively unchanged during plateau phase
  - Flat & iso-electric segment s

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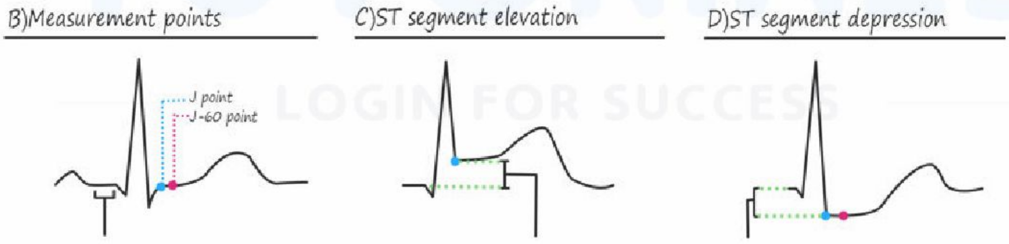

ST segment abnormalities

↓

ST elevation
ST depression } reference point → J joint

J60 – 60 milli second after J point
J80- 80 milli second after J point } more isoelectric

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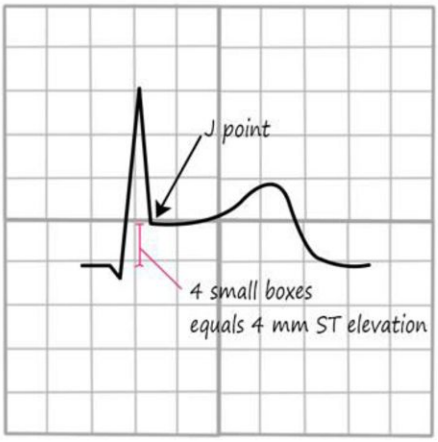
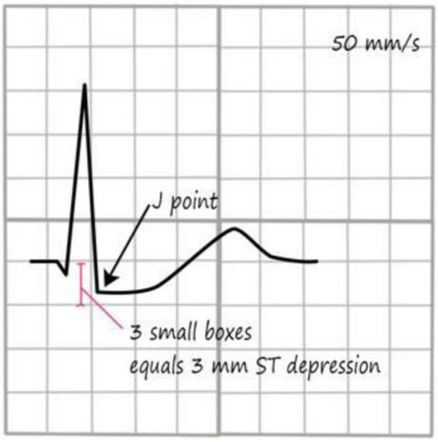


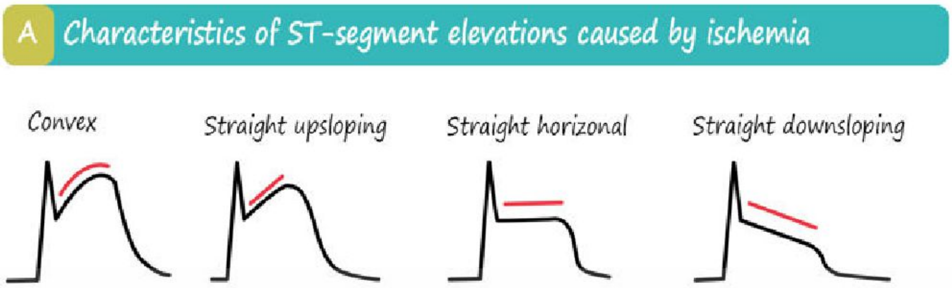


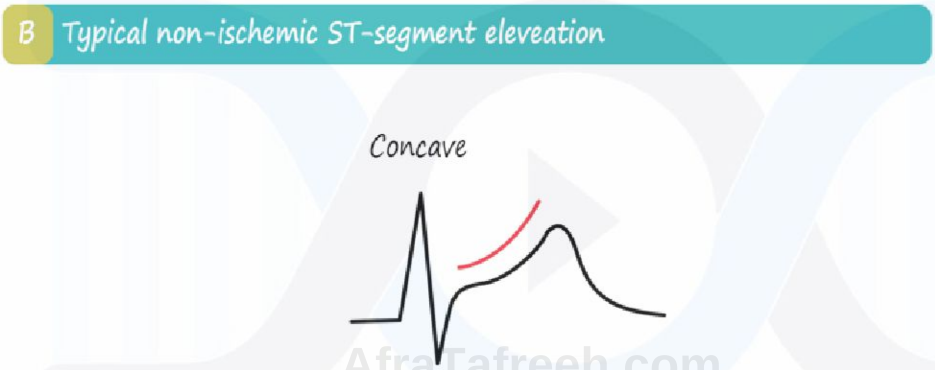
Electrocardiographic changes suggestive of Acute Myocardial Ischemia

ST- elevation	ST-depression and T wave changes
News ST- elevation at the J- point in two contiguous leads with the cut: ≥ 1 mm in all lead other than leads V2-V3 where the following cut points apply: ≥ 2 mm in men ≥ 40 years; ≥ 2/5 mm in men < 40 years, or ≥ 1.5 mm in women regarding of age	News horizontal or down- sloping ST- depression ≥ 0.5 mm in two contiguous leads and /or T inversion > 1 mm in tow contiguous leads with prominent R wave or R/S ratio < 1.

- All leads other than V2 & V3
- V2 V3 → St elevation

Male	Female
- > 40 years - > 2 mm	Irrespective o age > 1.5 mm
- < 40 years - > 2.5 mm	





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concave ST elevation

Less Lilley to be ischemic changes

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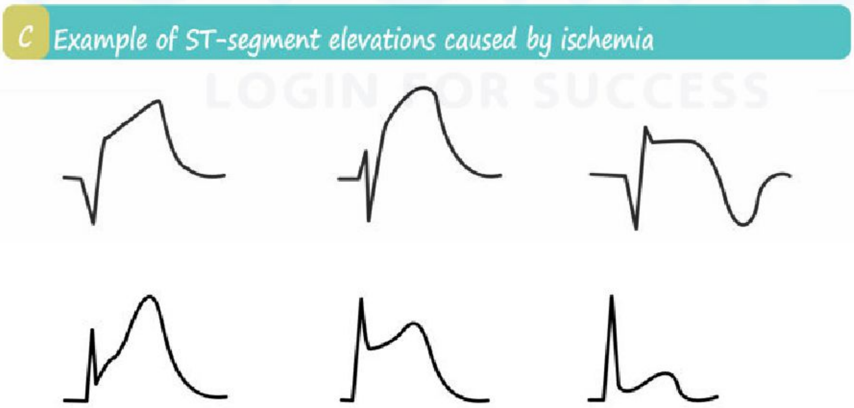

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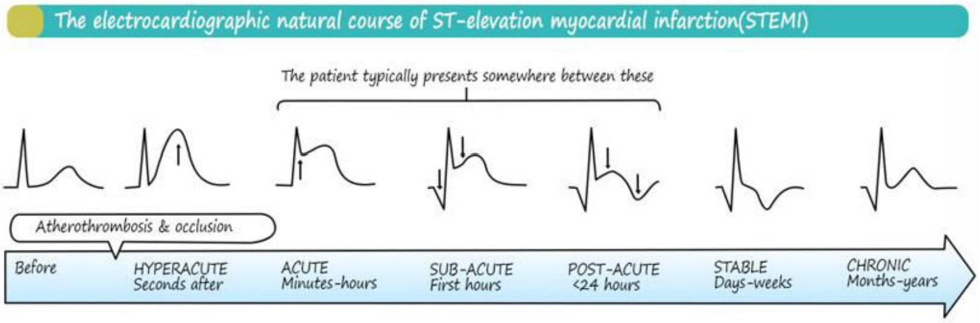

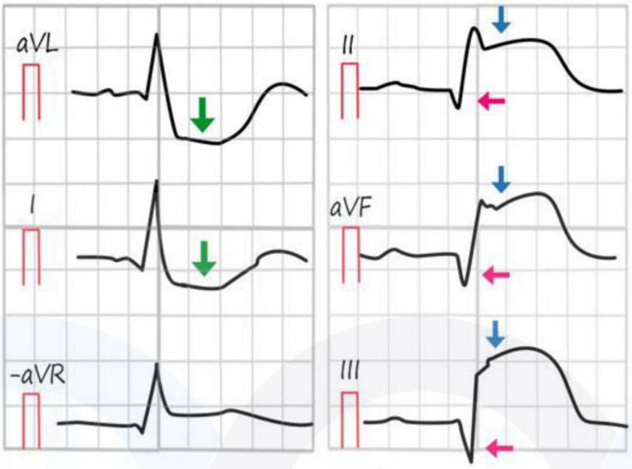

ST elevation in	Location in infarction
V_1 to V_4	Anteroseptal
V_1, V_1	Septal
V_3, V_4	Anterior
L_1, aVL	High Lateral
V_5-V_6 L_1 aVL	Lateral
V_3-V_6 L_1 aVL	Anterolateral
V_1 - V_6 L_1 aVL	Extensive Anterior
L_{II} L_{III} avF	Inferior
V_3RV_4 R	Right ventricular

- Transient ST elevation – Rest angina
  - Chronic heavy smokers
  - Vasospastic angina
  - Prinz metal's angina
- Time of pain: - midnight and 8:00 am-in the morning
- Occurs because of focal spasm of an epicardial coronary artery
- Treatment: - DOC: - calcium channel blockers –
  - Long-acting nitrate
  - Pain + → sublingual or i.v nitrates

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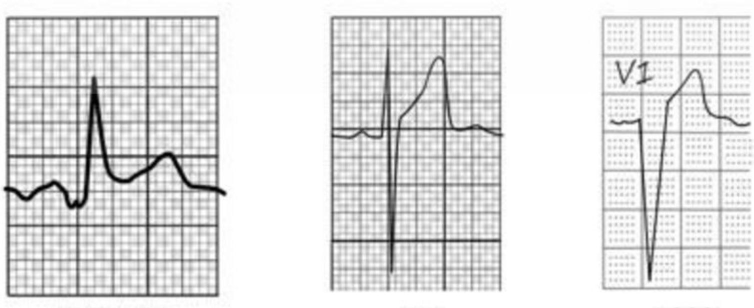

Pericarditis BER LBBB

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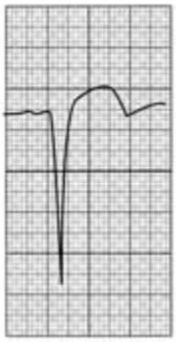
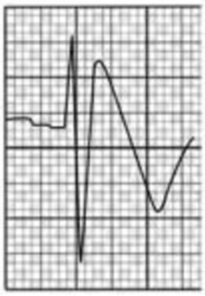
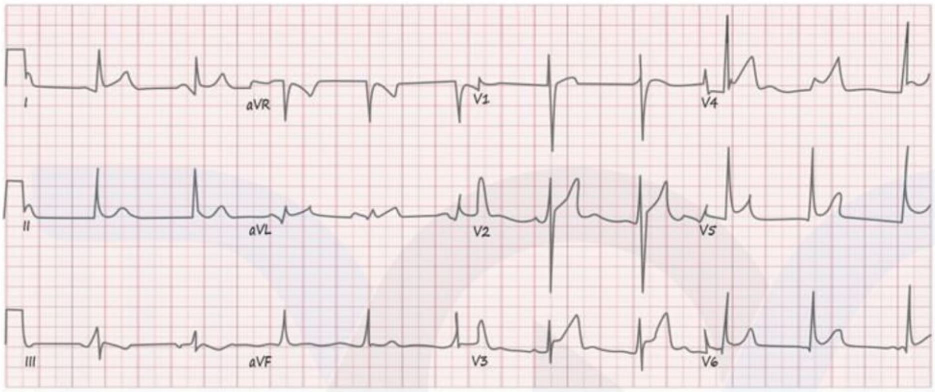


LV Aneurysm



Brugada



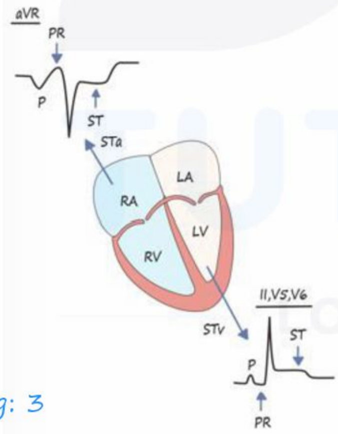
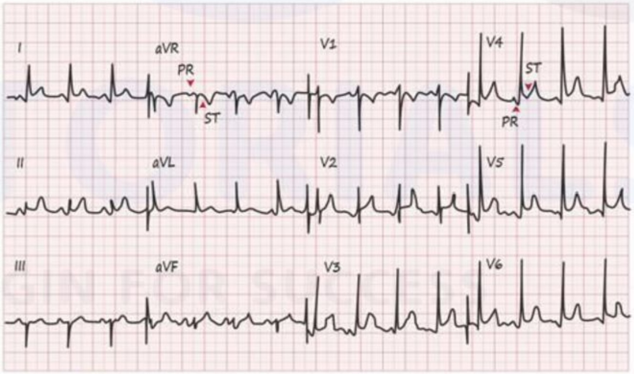
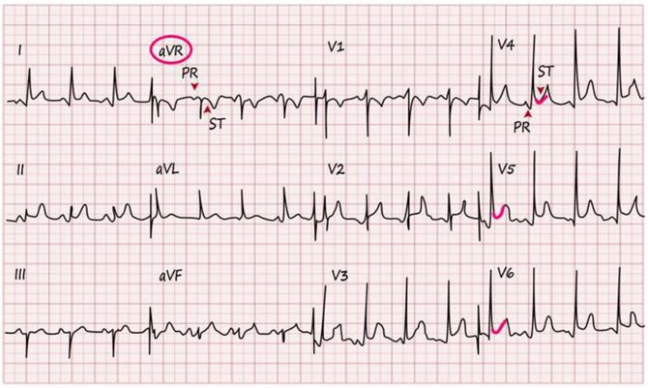
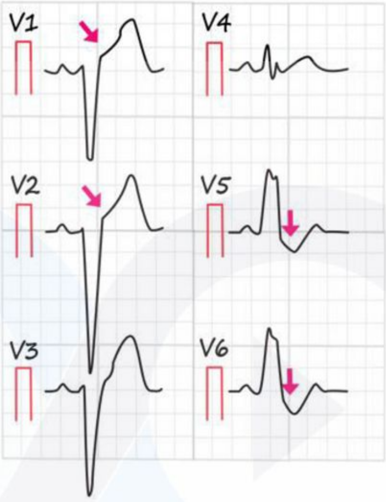


Fig: 3







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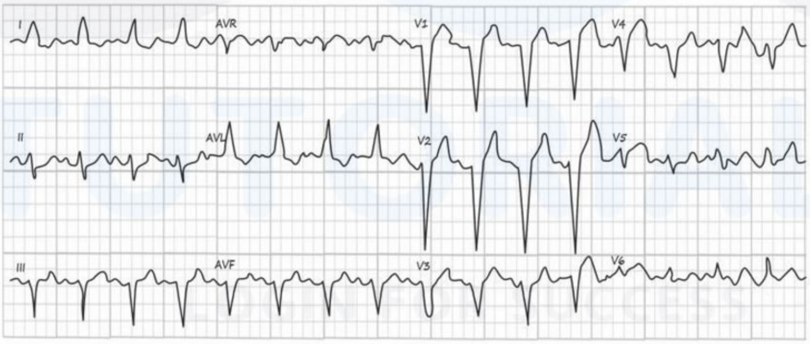

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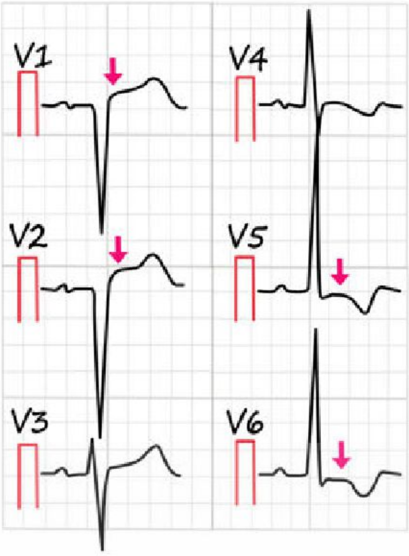
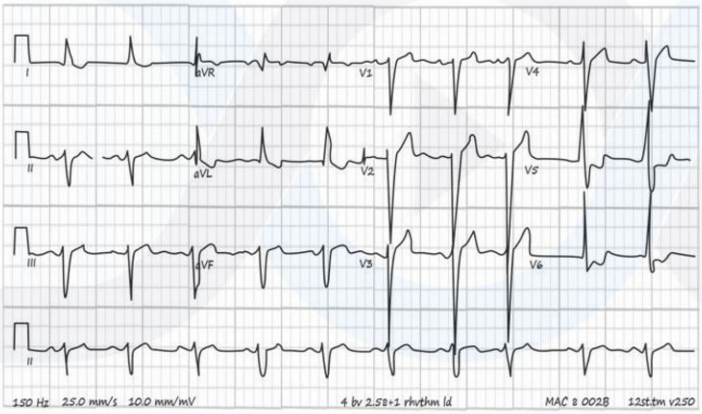
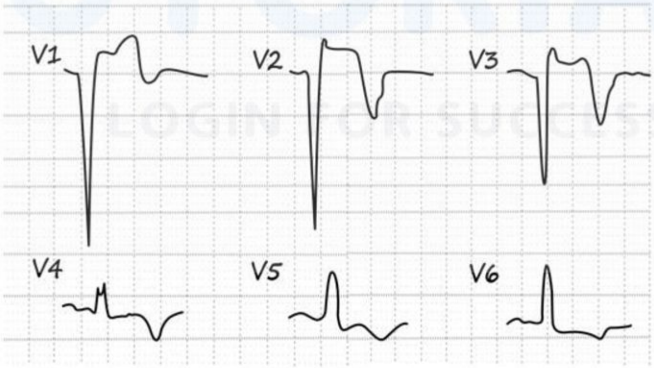
LVH-Secondary ST-T changes





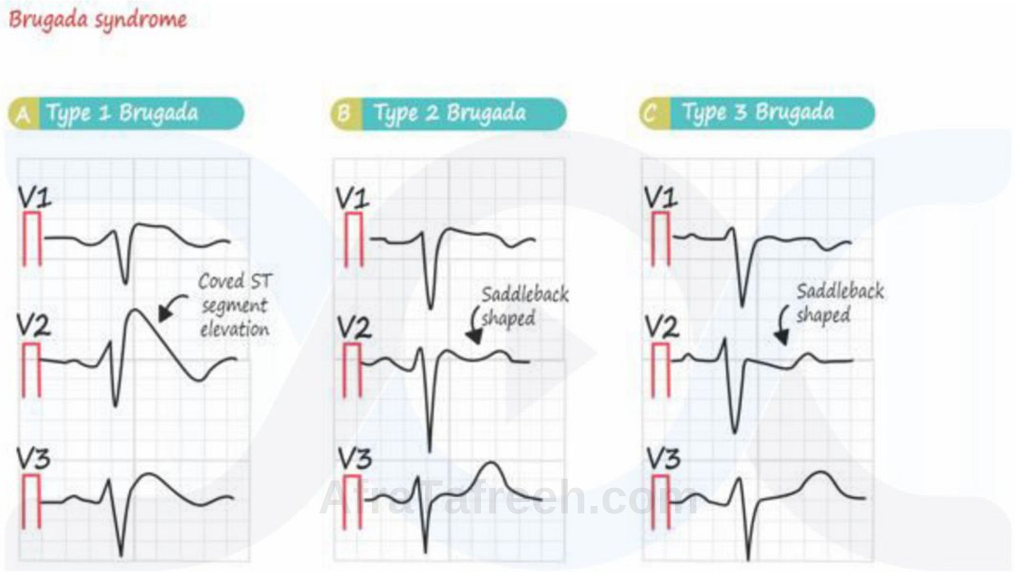


ST segment elevation

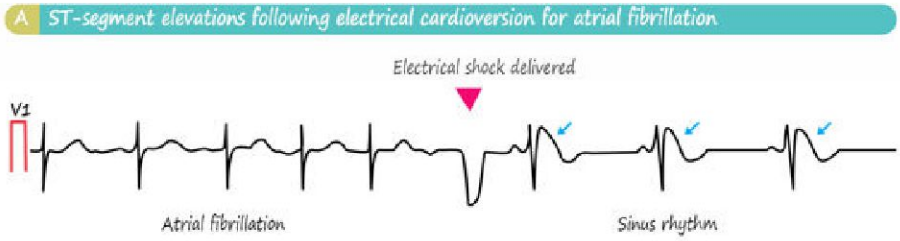
I V aneurysm

- ST elevation seen in > 2 weeks following an acute myocardial infraction

- Most commonly seen in the precordial leads
- May exhibit concave or convex morphology
- Usually associated with well-formed Q- or QS waves
- T-waves have a relatively small amplitude in comparison to the QRS complex (unlike the hyperacute T-waves of acute STEMI)



- Electrical Cardioversion – Transient ST segment elevation



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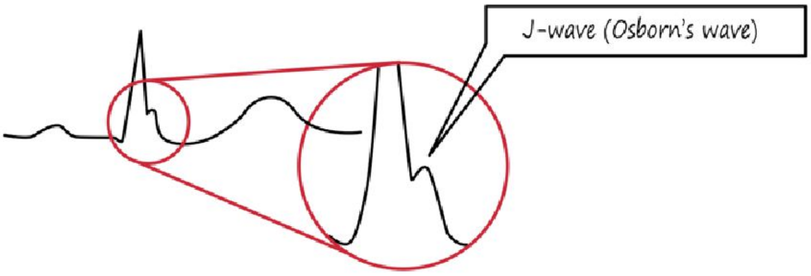
J-wave (Osborn's wave)



Osborn's wave → a/w hypothermia

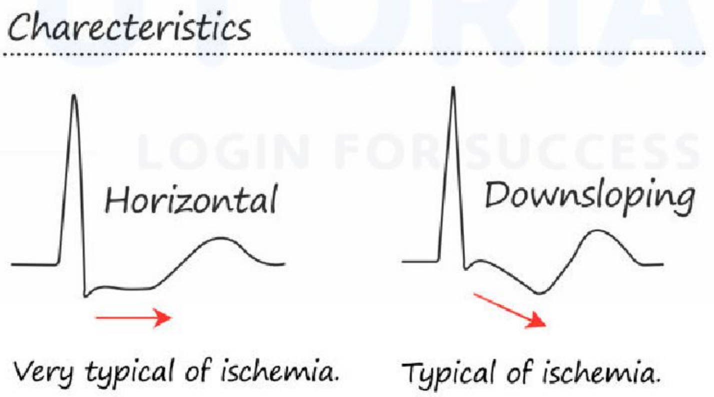
Differential Diagnosis of ST- Segment Elevation

- Ischemia/myocardial infraction
- Noninformation. Transmural ischemia (Prinz metal's angina, and probably Tako-tsubo syndrome, which may also exactly simulate classical acute infarction) Acute myocardial infarction
- Acute pericarditis
- Normal variants (including begin "early repolarize "pattern)
- Left ventricular hypertrophy /left bundle Brach block" other (rarer)
- Acute pulmonary embolism

- Brugada pattern (right bundle Brach block – like pattern with ST elevation in right precordial leads)
- Class 1 C antiarrhythmic drugs
- DC cardioversion
- Hypercalcemia
- Hypokalemia
- Hypothermia (K [Osborn] waves)
- Nonischemic myocardial injury
  - Myocarditis
  - Tumor invading left ventricle
  - Trauma to ventricles
- Usually localized to V1-V2 or V3

St segment depression→ with reference to J point

- Myocardial ischemia



- Pattern of ST depression- upsloping, Horizontal, Down sloping – ischemic ST depression

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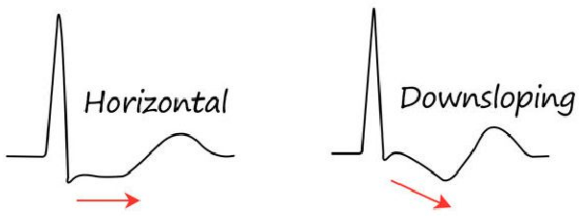
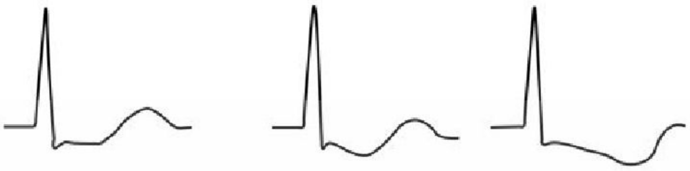
Charecteristics



Very typical of ischemia. Typical of ischemia.



Horizontal depression with distinct ST-segment. | Downsloping with positive T-wave | Downsloping with inverted T-wave | Horizontal depression with short ST-segment.

(ST- T changes)

exercise hyperventilation

(ST- T changes)
→ exercise hyperventilation } upsloping ST depression

de winter's sign

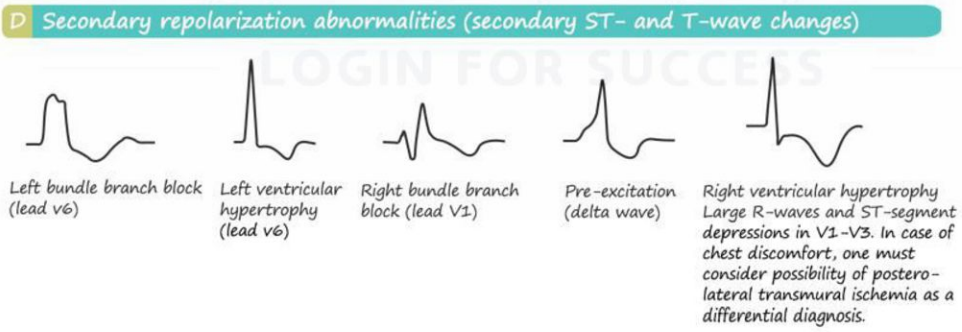
Proximal LAD occlusion

- Upsloping ST depression
- Tall T waves

de winter's sign

secondary ST segment depression occur in the following conditions:

- Left ventricular hypertrophy
- Right ventricular hypertrophy
- Left bundle branch block
- Right bundle branch block
- Pre-excitation



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Hypokalemia: - Flat t waves

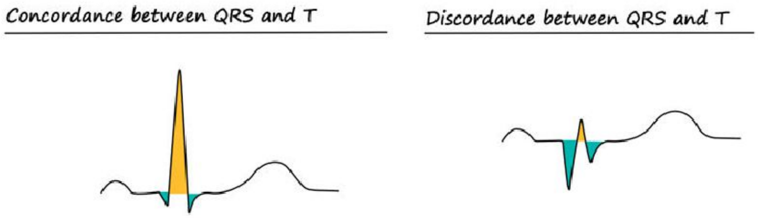
U waves

ST segment depression

Concave St depression – Digoxin

Analysis of T wave

- Produced by the rapid phase of ventricular repolarization
- Positive in most precordial leads & Limb leads
- Almost always inverted in lead aVR, usually in lead V1& sometimes in lead III
- Does not exceed 5 min in height in the limb leads and 10 min in precordial leads



Net QRS deflection positive

A Normal T-waves

Normal T wave Normal variant

N t wave – slightly symmetric

-descending limb – steeper

T waves abnormalities

B Large T-waves

Hyperkalemia Hyperacute T wave

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pointed t waves

Narrow vase

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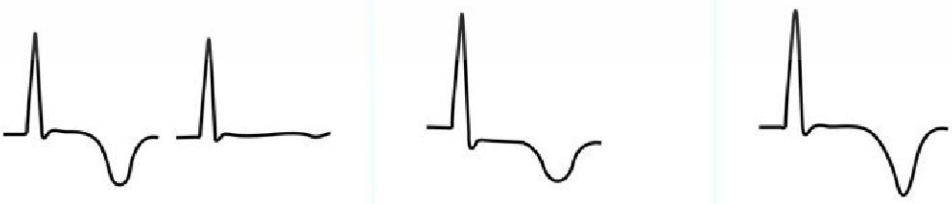
- not very pointed'
- Base more wide
- STEMI
- Prinz metal angina

C Biphasic (diphasic T-waves)

D Negative (inverted) T-waves



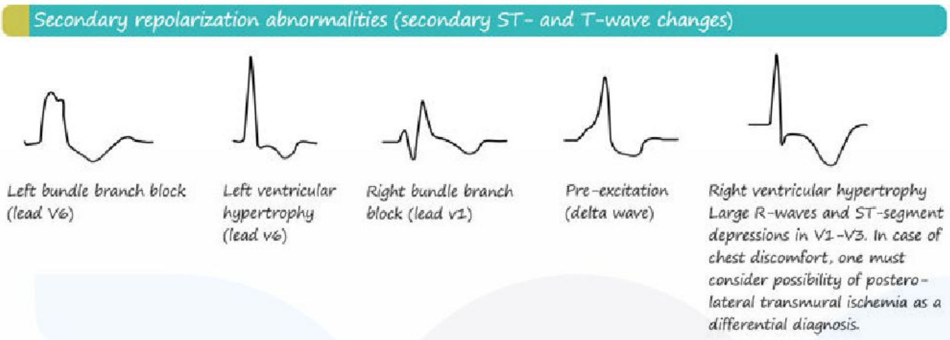
- Post ischemia – located t wave inversion

- Cerebrovascular insult → ICH

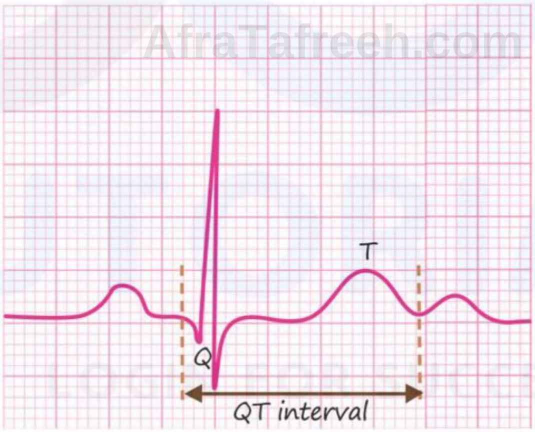
  SAH

  cerebral T waves

  Large inverted t waves



Analysis of QT internal 01:03:58



- Qt interval: - beginning of QRS complex to end of T wave

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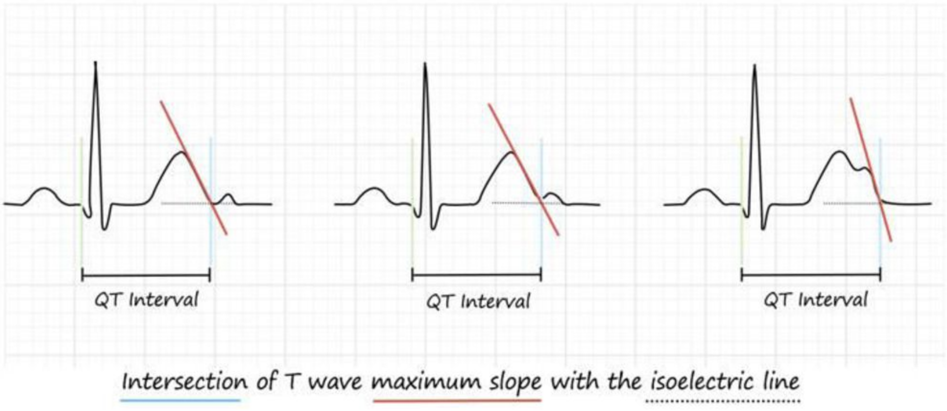


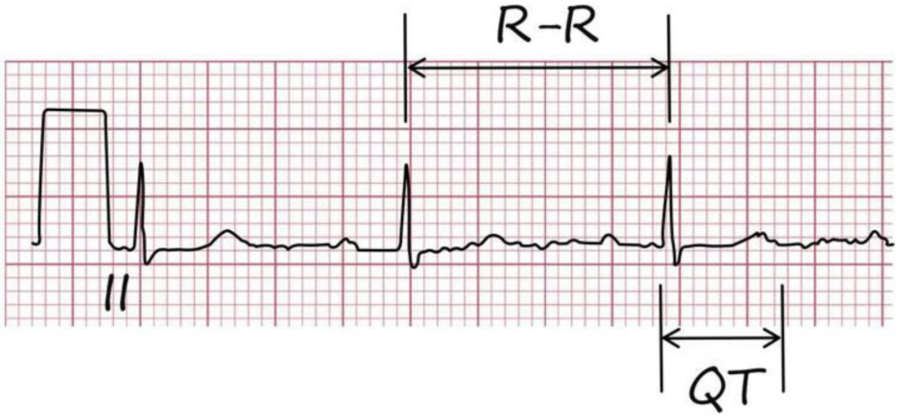
- Reflects the duration of the ventricular action potential
- Rate -related changes in the duration of the normal ventricular action potential
- Upper limit for QTc (in milliseconds) sis 460 for women and 450 for men. Lower limit 390
- QT dispersion
  - HR increase – QT shortens
  - HR decrease – QT lengthens

Corrected QT interval (QTC)

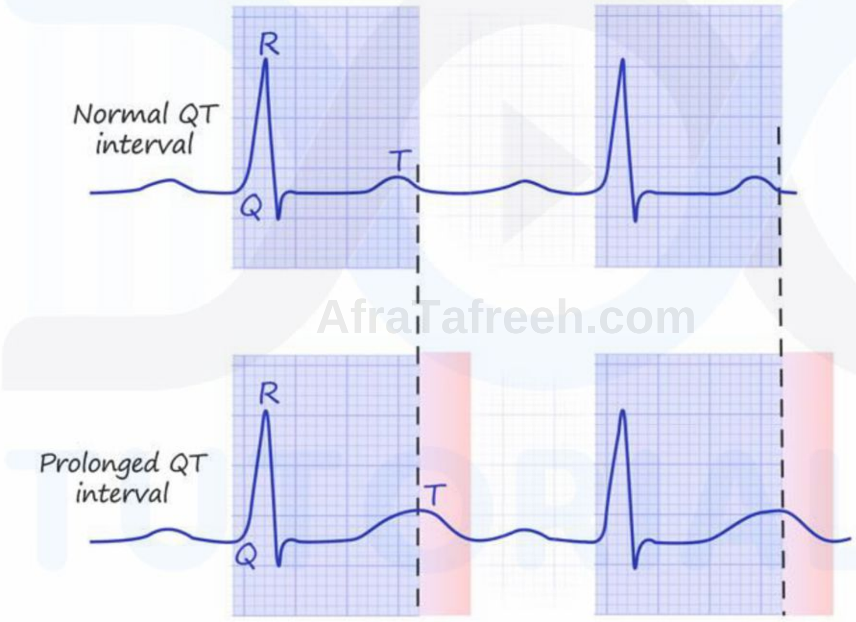
- Bazetts' formula $= \frac{QT}{\sqrt{RR \text{ interval}}}$

HR= 60/min

QTC = QT



- Normally QT, interval should be less than ½ of the preceding R interval



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- Bazett formula: QTc + QT/ √RR
- Fridericia formula: QTc + QT/RR 1/3
- Framingham formula: QTc= QT+ 0.154(1-RR)
- Hodge's formula: QTc+ QT + 1.75 (heart rate – 60)

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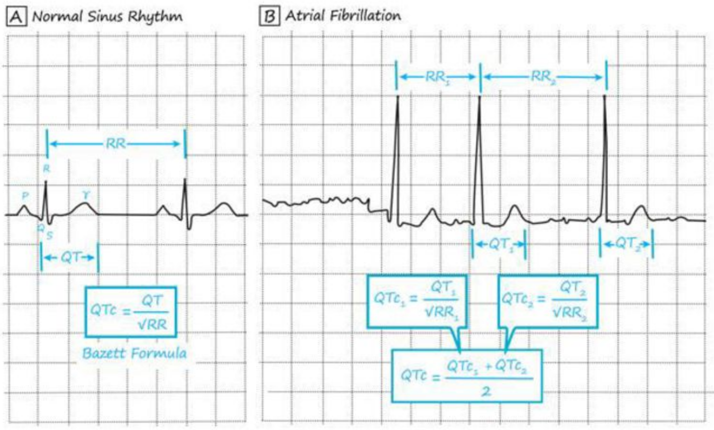

Abnormalities of QT interval

Long QT interval → Risk of arrhythmias & sudden death

Congenital	Acquired
-Jerval Lange Nielson syndrome → AR	- Drugs
-Romano ward syndrome → ad → Without deafness	- Electrolyte abnormalities: Hypokalemia, Hypomagnesaemia, hypocalcemia

Drugs Associated with QT Prolongation and TdP

Antiarrhythmics	Antimicrobials	Antidepressants
Amiodarone	Levofloxacin	Amitriptyline
Sotalol	Ciprofloxacin	Desipramine
Quinidine	Gatifloxacin	Imipramine
Procainamide	Moxifloxacin	Doxepin
Dofetilide	Clarithromycin	Fluoxetine
Ibutilide	Erythromycin	Sertraline
	Ketoconazole	venlafaxine
	Itraconazole	

Antipsychotics	Others
Haloperidol Droperidol Quetiapine Thioridazine Ziprasidone	Cisapride Sumatriptan Zolmitriptan Arsenic Dolasetron Methadone

Short QT interval

- Electrolyte abnormalities: - Hyperkalemia
  - Hypercalcemia
- Acidosis
- Hyperthermia
- Digitalis effects

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→ can predispose to arrhythmias (VF, AF) and sudden cardiac death

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HEART SOUNDS

- Brief auditory vibrations
- Caused by blood flowing through cardiac chambers

Description of heart sounds 00:02:41

- Intensity – Loud and soft
- Pitch -High and low
- Location
- Timing in relation to cardiac cycle

High pitched sounds

- S_1
- S_2
- Opening snap
- Ejection clicks
- Pericardial knock
- Prosthetic valve sounds

Loud pitched sounds

- S_3
- S_4
- Tumor plop

First heart sounds 00:06:41

- Referred to as 'Lub' sound
- Occurs at the onset of ventricular systole
- Results from closure of mitral and tricuspid valve
- Actual reason: - tensing of valve leaflets and chordae tendinae after valve closure
- Coincides with carotid pulse
- Best heard at apex
- 2 components → M_1 component
  T_1 component
  - M_1 louder than T_1
  - M_1 best heard at apex
  - T_1 best heard at lower Left sternal border
  - Best heard with diaphragm
- Mitral valve leaflet
  - Anterior: 3 times broader and freely mobile
  - Posterior

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Intensity of S_1 factors

- Position of mitral valve leaflet when LV begins to contract
- Leaflet mobility and structural integrity
- Force of LV systolic contraction
- Depends on PR interval
- Depends on chest wall thickness

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Position of mitral valve leaflet

- Normally – end of diastole

  ↓

  Mitral valve floating – semi closed position
- At onset of systole – mitral valve wide or partially open

Valve leaflet mobility and structural integrity

- Fibrosed and calcific anterior mitral leaflet – soft S_1

LV Contractility

- Higher force and speed of LV contraction

  ↓

  Loud S_1

PR interval

- Part of diastole
- Longer PR interval – long diastolic filling time

  ↓

  Soft S_1

Chest wall thickness

- Obese → Soft S_1
- Thin → Loud S_1

Loud S_1

- Short PR interval
- Tachycardia

- Thin chest wall
- Conditions with increased cardiac output (large stroke volume)
- Mitral stenosis
- Lift atrial myxoma
- Atrial septal defect

- In mitral stenosis, the loudness of S_1 is not related to severity
- Mobility of the valve that determines loudness

Soft S_1

- Obesity
- Emphysema
- Pericardial effusion
- Conditions associated with long PR interval
- Low cardiac output
- Low LV systolic function
- Rheumatic MR
- Acute AR
- Myocarditis

Variable S_1

- Atrial fibrillation
- Complete heart block

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Splitting of S_1

- Between M_1 and T_1 – narrow gap of 20 – 30 millisecond
- Heard as a single sound
- RBBB

  ↓

  Delayed activation of Right ventricle

  ↓

  Tricuspid component occurs later → splitting

  ↓

  Appreciated at lower left sternal border
- Ebstein anomaly

Second heart sounds 00:32:46

- Known as "dub"
- Louder and higher pitch than S_1
- Occurs at the end of ventricular systole
- Vibrations associated with closure of aortic and pulmonary valve
- 2 components → A_2 and P_2
- Normal splitting of S_2 is due to more time delay of RV ejection
- During inspiration → Prominent split
- During expiration → split disappears
- A_2 component louder than P_2
- A_2 component – Pressure difference across aortic valve

  In case of systemic HTN – loud A_2

  In case of pulmonary HTN – loud P_2

Intensity of A_2 depends on

- Aortic pressure
- Size of aortic root
- Mobility and structural integrity of aortic valve
- Relative proximity of aorta to chest wall

Intensity of P_2 depends on

- Pulmonary artery pressure
- Size of pulmonary artery
- Mobility and integrity of pulmonary artery

- P_2 – soft sound in pulmonary area
- All areas including pulmonary area A_2 louder than P_2

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Loud P_2

- In pulmonary area, P_2 higher intensity than A_2

Individual components heard

- Second left interspace close to sternal border
- Patient in supine position
- During inspiration

  ↓

  – Lower the intra thoracic pressure

  – Increased pulmonary vascular capacitance

  – Prolongs RV systole duration → delay P_2

  – Reduced blood flow to LA and LV → early A_2

  – Split widens

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Abnormalities of S_2 splitting

- Wide and fixed split of S_2

  ↓

  - No respiratory variation
  - ASD
  - Prolonged RV failure
- Why there is wide split in S_2 in ASD?
  - Prolonged RV ejection → Delayed P_2
- Why there is a fixed split?
  - No differential filling
  - Pressure equalization between both atria throughout the respiratory cycle

Wide split with Normal respiratory variation

- RBBB – delay in RV emptying

Paradoxical split / reversed split

- Delay in LV emptying
- Delayed A_2
  - LBBB
  - Severe aortic stenosis
  - Severe LVF

Single S_2

- Absence of either of A_2 or P_2 component
- Fusion of A_2 and P_2 without respiratory splitting

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Absent A_2

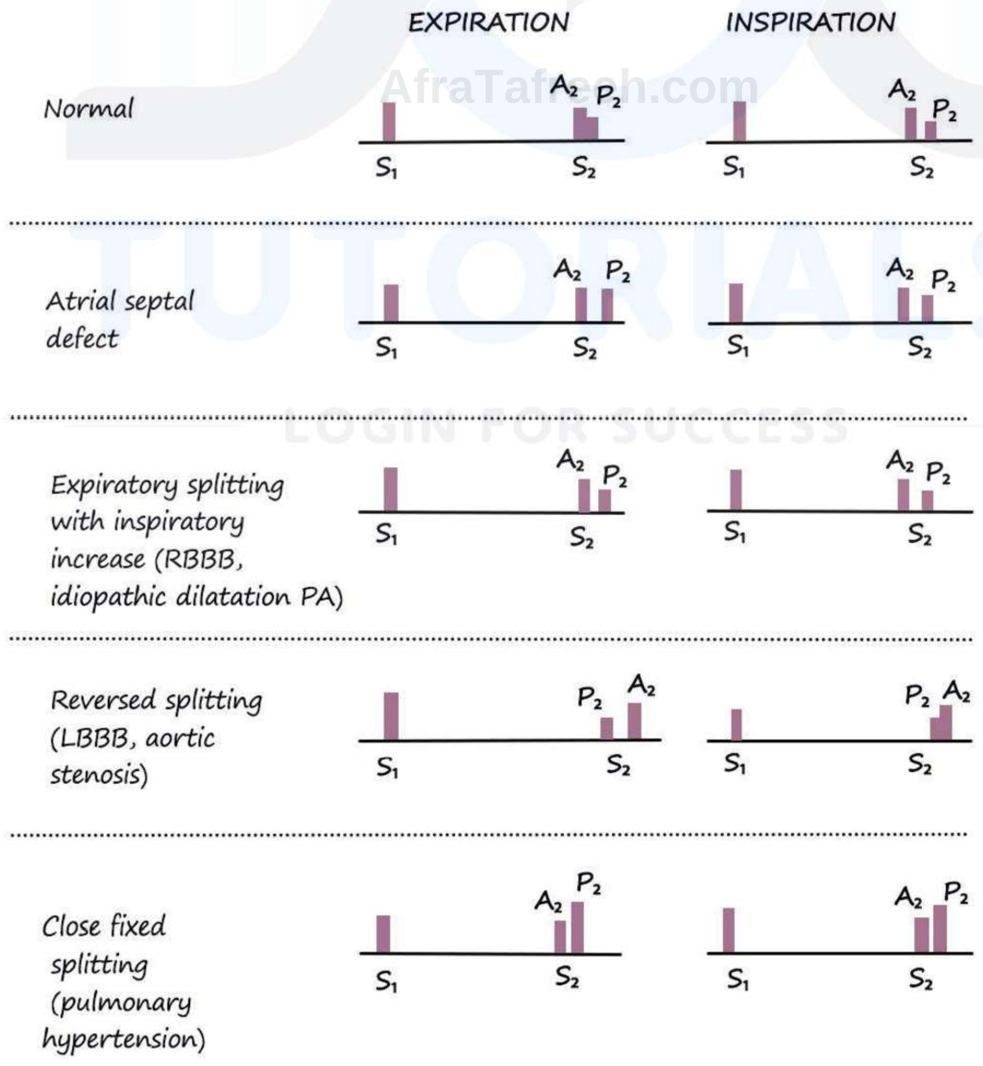
- Severe calcific as with immobile aortic valve
- Severe AR due to valve destruction

Absent P_2

- Congenital absence of pulmonary valve
- Pulmonary atresia
- Severe pulmonary stenosis

Aortic stenosis

- Delayed A_2
- Subsequent fusion



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Third heart sounds 00:57:55

- Low pitched
- Early diastolic sound
- Best heard with bell over apex
- Coincides with rapid ventricular filling with opening of AV valves

Physiologic S_3

- Children
- Young adults
- Pregnancy
- Beyond 40 years → S_3 is abnormal

Common causes of S_3

- LVF – early sign
- Mitral regurgitation → because of volume overloading of ventricles
- Heart failure: - S_3 with tachycardia → Gallop rhythm

LVS_3	RVS_3
- Mitral area - Increase on expiration	- Tricuspid area - Increase on inspiration

Fourth heart sounds 00:57:55

- Soft and low-pitched sound
- Best heard with bell of stethoscope over apex
- Occurs just before S_1
- Always pathological
- Due to forceful atrial contraction against a stiff non – compliant ventricle

Causes of LVS_4	RVS_4
– HTN – Myocardial infarction – Severe AS – Acute MR – Cardiomyopathy	– Pulmonary HTN – Pulmonary stenosis

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TACHYARRHYTHMIAS

Introduction

- Tachyarrhythmias are divided into
  - Supraventricular
  - Ventricular

Supraventricular tachyarrhythmias 00:01:22

- Driving circuit – Above the level of ventricle
  - Sinus node
  - Atria
  - AV node
  - Bundle of His
- Electrophysiological substrate – Above bundle of his
- Less likely to cause Hemodynamic compromise

Ventricular tachyarrhythmias 00:03:44

- Driving circuit – Ventricular tissue or purkinje fibers
- They require immediate attention
  - They can result in profound hemodynamic compromise
  - Much poorer prognosis
  - Indicates presence of significant underlying heart disease

Narrow complex Tachycardia 00:07:36

- Supraventricular origin
- QRS duration < 120 milli seconds
- Ventricular activation is via normal His purkinje system

Wide complex Tachycardia 00:09:36

- Usually - Ventricular in origin
- Rare scenarios - SVT
  - SVT with bundle branch block
  - SVT in pre-excited tachycardia

Mechanism of Tachyarrhythmias 00:13:04

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- Re- entry Phenomenon
- Automaticity → decrease in excitation threshold of pacemaker
- Triggered activity → After depolarization

After Depolarisation - Before full repolarisation, repeat depolarisation in an area

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CLASSIFICATION OF SVT

- 2 groups
  - Physiologic Sinus Tachycardia
  - Pathologic SVT

Pathologic SVT 00:01:33

- Classified into 3 groups → Tachycardias originating from atrium
  → AVNRT (AV nodal re-entry tachycardia)
  → Tachycardias associated with accessory atrio-ventricular pathways

Tachycardias originating from atrium 00:03:50

- Inappropriate sinus tachycardia
- Focal atrial tachycardia
- Multifocal atrial tachycardia
- Atrial fibrillation
- Atrial flutter

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Paroxysmal supraventricular tachycardia (PSVT)

00:05:40

- Characterized by sudden onset and termination
  - AVNRT
  - AV Re-entry via accessory pathway
  - Atrial tachycardia

Clinical presentation

- Palpitation
- Chest pain
- Dyspnea
- Syncope

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Diagnosis:

- ECG done at the time of symptoms

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Treatment

- Based on What is the arrhythmia?
- Hemodynamic effect?

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SINUS TACHYCARDIA

- Increased rate of depolarization from SA node
- Location of SA node: - Superior aspect of crista terminals
- Rate > 100/min
- Symptomatic stimulation and Vagal withdrawal

Sinus P waves 00:02:50

- Positive in leads II, III and avF
- Negative in avR
- Initially positive biphasic in V1

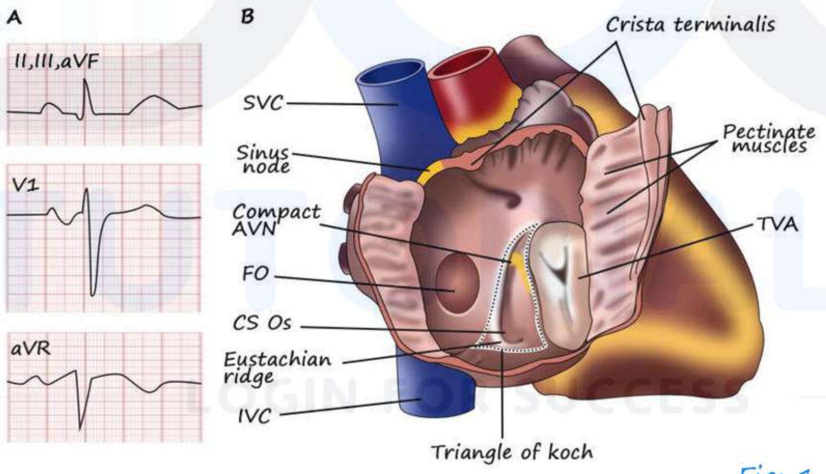

Fig: 1

Sinus Tachycardia

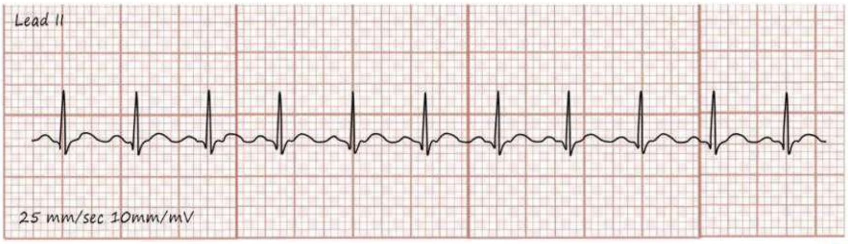

Fig: 2

Sinus Tachycardia 00:05:00

- Sinus tachycardia can be – Physiological
  – Non physiologic

Etiology 00:05:38

- Exercise
- Fever
- Anemia
- Thyrotoxicosis
- Sympathomimetic/Vagolytic drugs
- Phaeochromocytoma
- If there is abrupt onset and offset → consider about Focal atrial tachycardia
- Treatment : – treat physiologic cause

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Non physiologic sinus tachycardia 00:09:38

- Spontaneous increase in sinus rate at rest
- Out or proportion to the level of exertion
- Occurs due to Autonomic dysregulation
- Females > males
- Age group: – 3rd or 4th decade of life

Clinical feature

- Palpitations
- Chest pain
- Syncope

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Treatment

- Calcium channel blockers
- Beta blockers
- Ivabradine

Postural Orthostatic Tachycardia syndrome

00:13:10

- POTS
- Consists of Orthostatic Hypotension + Sinus Tachycardia
- Symptomatic sinus tachycardia that occurs with postural change
- Autonomic dysfunction

Clinical feature

- Palpitation
- Chest pain
- Syncope

Treatment

- Salt supplementation
- Oral fludrocortisone
- Midodrine

FOCAL ATRIAL TACHYCARDIA

- Also referred to as Atrial ectopic tachycardia
- Arises from a single site within Left/Right atrium
  - Atrial flutter
  - Atrial fibrillation
- Usually paroxysmal and self-limited
- If there is continuous focal atrial tachycardia- it is called as Incessant Atrial Tachycardia associated with left ventricular dysfunction

Mechanism 00:03:51

- Abnormal automaticity
- Triggered activity
- Micro-entry → confined to atrium
- In almost 2/3 cases → foci of origin – Right atrium
  - Tricuspid annulus
  - Crista terminals
  - Coronary sinus ostium
  - Around pulmonary veins
- may or not be associated with structural heart disease
- associated with – cardiomyopathies
  - Hypertension
  - Prior catheter ablation → atrial fibrosis ↓ nidus for atrial tachycardia

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Symptoms 00:08:49

- Palpitation
- Incessant AT- Tachycardia induced cardiomyopathy

Diagnosis 00:09:54

- ECG
- Paroxysmal Nature

ECG features

- Atrial rate: - 150-200/min
- P- wave morphology – normal or abnormal

↓

V1 & lead II

- Left atrial focus → Positive or biphasic P wave in V1
- Right atrial focus → Negative P wave in V1
- Atrial septum → Narrow P wave duration

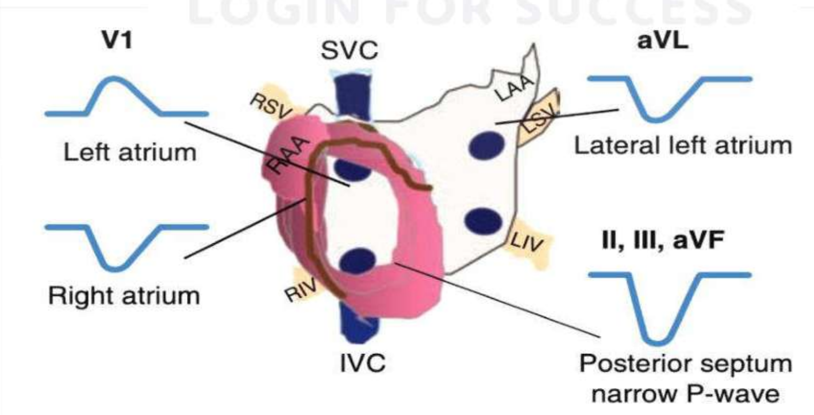
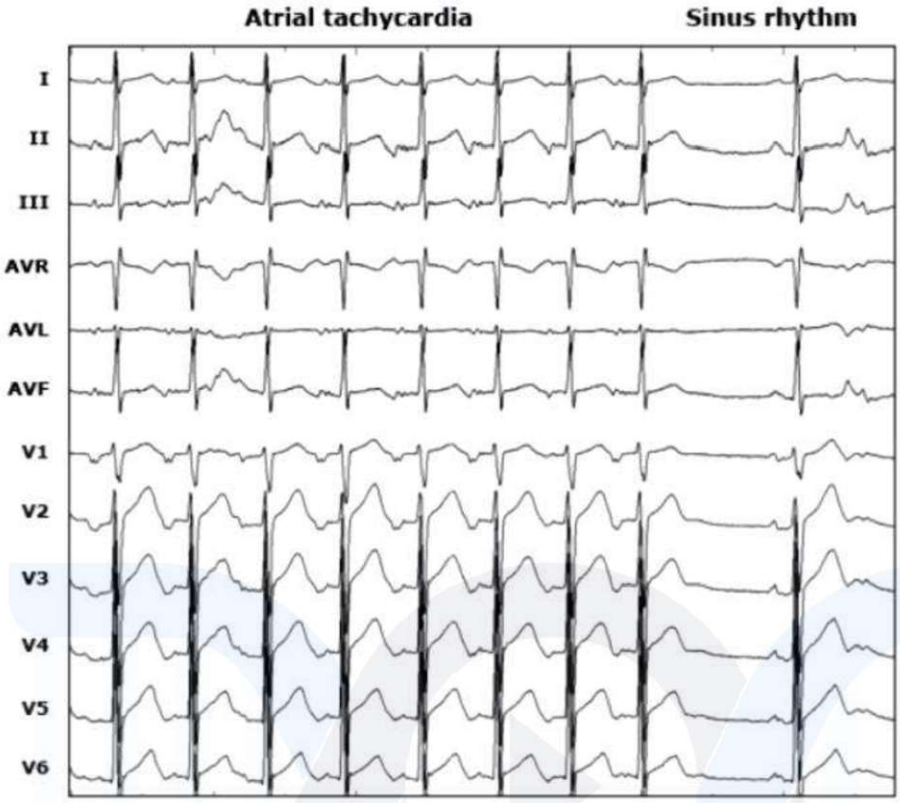


Fig: 1

- Isoelectric base line
- QRS morphology



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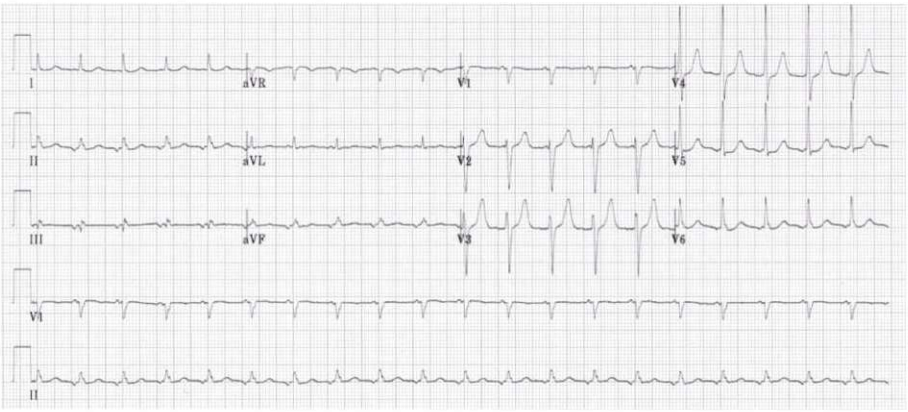
- AT classically have 1:1 AV conduction (each impulse is conducted to ventricles)
- AT with block occurs in Digitalis toxicity
- PR interval Normal
- Long RP/PR Interval

→ distinguish focal atrial tachycardia from other SVT



Consistent P Wave morphology is seen

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Management 00:20:54

- Treatment response varies based on mechanism

Atrial tachycardia due to re- entry

- Vagal maneuver
- Adenosine

→ transient AV block without terminating arrhythmia

Atrial tachycardia due to triggered activity

- Adenosine → arrhythmia terminated

Hemodynamically stable symptomatic Atrial Tachycardia

- Acute Treatment - Oral or IV Beta blockers /CCB → diltiazem, verapamil
- Failed drug response: consider ablation

Hemodynamically unstable Atrial Tachycardia

- Electrical Cardioversion
- Intravenous Amiodarone- Chemical Cardioversion

Frequent symptomatic AT

- Long term/Chronic management: - Beta blockers, CCB
- Failed drug response : Catheter ablation

AVNRT

AV modal re – entry tachycardia (AVNRT)

- Regular SVT
- Abrupt onset and offset – PSVT
- Most common PSVT
- AVNRT → 60% for catheter ablation
- Usually affects young healthy women (2nd – 4th decade)
- Majority of patients → no underlying structural heart disease
  - Some may have underlying
    - Pericarditis
    - Previous MI
    - MVP (Mitral Valve Prolapse)

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Anatomic basis of Tachyarrhythmia 00:03:32

- Re-entry tachyarrhythmia → coexistence of slow and fast pathways in AV modal tissues
- Certain dual pathways involving AV mode

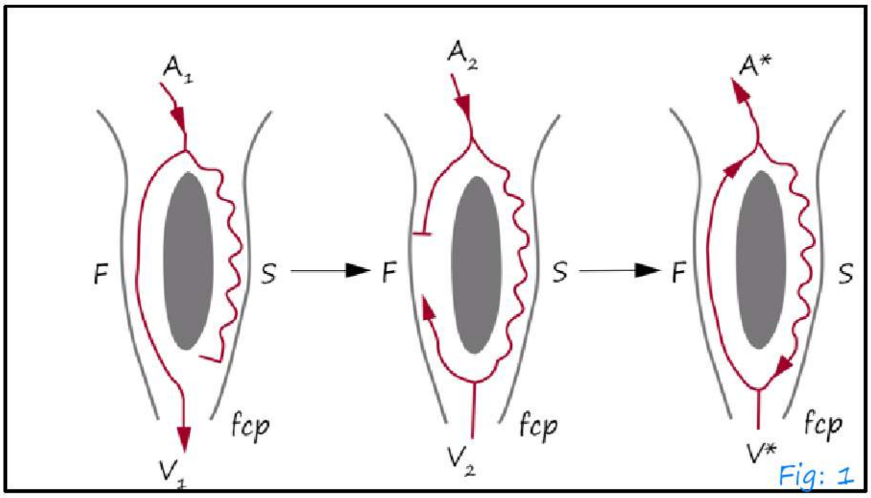

Fig: 1

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- There are 2 pathways
  - Slow pathway – S
  - Fast pathway F
- S and F pathway finally come to FCP
- F pathway
  - Conducts rapidly
  - Has relatively long refractory period
- S pathway
  - Conducts slowly
  - Has short refractory period
- During normal sinus rhythm, the impulse enters AV node
- Impulse actually travels both in fast and slow pathway
- By the time, slow pathway reaches the final common pathway, there occurs a refractory period of impulse.

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Types of AVNRT

- Typical
- Atypical

Typical AVNRT 00:10:15

- Common form (80%)
- Also referred to as slow fast AVNRT

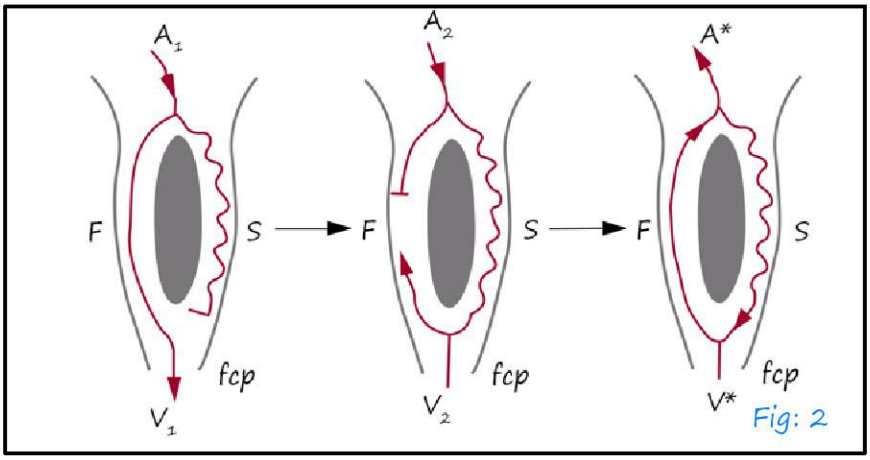

Fig: 2

- Requires a critically timed PAC (premature atrial complex)
- If the impulse reaches when the fast pathway is in refractory period → forward progression through fast pathway is blocked
- Slow pathway conducts premature atrial beat
- PR interval of pre-mature beat → longer
- If the fast pathway has recovered its excitability in the refractory period, impulse connects in retrograde fashion also.
- There is anterograde conduction down the slow pathway and retrograde conduction up the fast pathway and subsequently cycle gets repeated → sustained tachycardia

Atypical AVNRT 00:16:10

- 20% cases of AVNRT – atypical
- Antegrade conduction via fast pathway
- Retrograde conduction via slow pathway

↓↓

Fast – slow – AVNRT

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Clinical manifestations 00:17:43

- Palpitation
- Dizziness
- Syncope
- Dyspnea
- Chest pain
- JVP – cannon a wave
- Elevated venous pressure – release of natriuretic peptide

  ↓

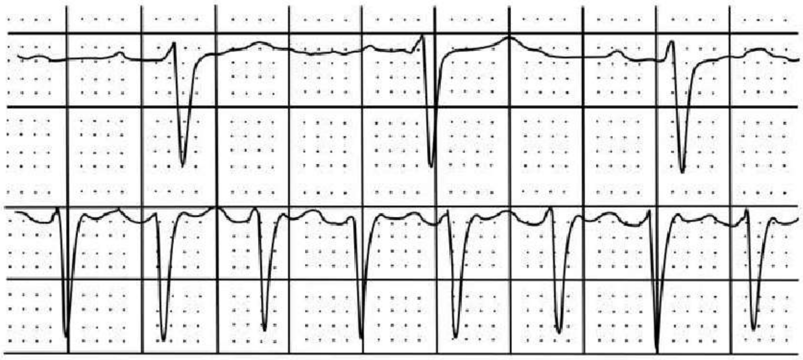
  Responsible for post tachycardia diureris

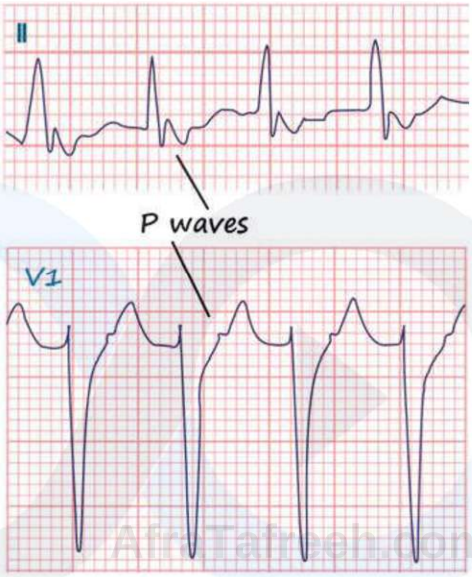
ECG Characteristics 00:20:17

- Ventricular rate: - 120 – 220 beats / minutes
- Abrupt onset following a PAC
- PAC – prolonged PR interval
- Typical AVNRT – short RP tachycardia

  Atypical AVNRT – long RP tachycardia
- In a typical AVNRT – P wave buried or fused within QRS
- P wave after QRS – pseudo R_1 in lead,

  Pseudo S in inferior leads





- Atypical AVNRT → P wave occurs very late after QRS

Treatment of AVNRT 00:26:51

- First line → vagal maneuvers → carotid sinus massage
  → Valsalva maneuver
- Failed vagal maneuver → adenosine 6-12 mg iv
- Failed vagal and adenosine → iv verapamil/ Diltiazem
- β – blockers →
- if patient has hemodynamic compromise –DC cardioversion

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Prevention of recurrence 00:31:31

- long term treatment → Drugs → calcium channel blockers β blockers

  → catheter ablation

  ↓

  > 95% cases respond to catheter ablation.

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AVRT

Tacchycardias associated with accessory AV pathways

- Orthodromic AV re-entry tachycardia (Orthodromic AVRT)
- Pre-excited Tachycardias

Accessory pathways (Bypass tracts) 00:02:11

- They are abnormal connections consisting of fibres that connect atrium / AV node to ventricle
- Occur 1 in 1500-2000
- Can be associated with
  - Narrow complex tachycardia
  - Wide complex tacctycardia
- There abnormal connections have embryologic basis

  ↓

  Because of failure of complete partitioning of atrium and ventricle by the fibrous AV rings
- Most individuals have structurally normal heart
- May be assosiated with :
  - Ebstein anomaly
  - Fabry's disease
  - Danon's disease
- Most frequent location of accessory pathway → Between LA and free wall of LV
- Pathways are also located in

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- Posteroseptal region
- Right ventricular free wall
- Anteroseptal region

- Pathways can be anterograde or retrograde
- These pathways can act as potential triggers
- When there is antegrade condition via accessory pathway

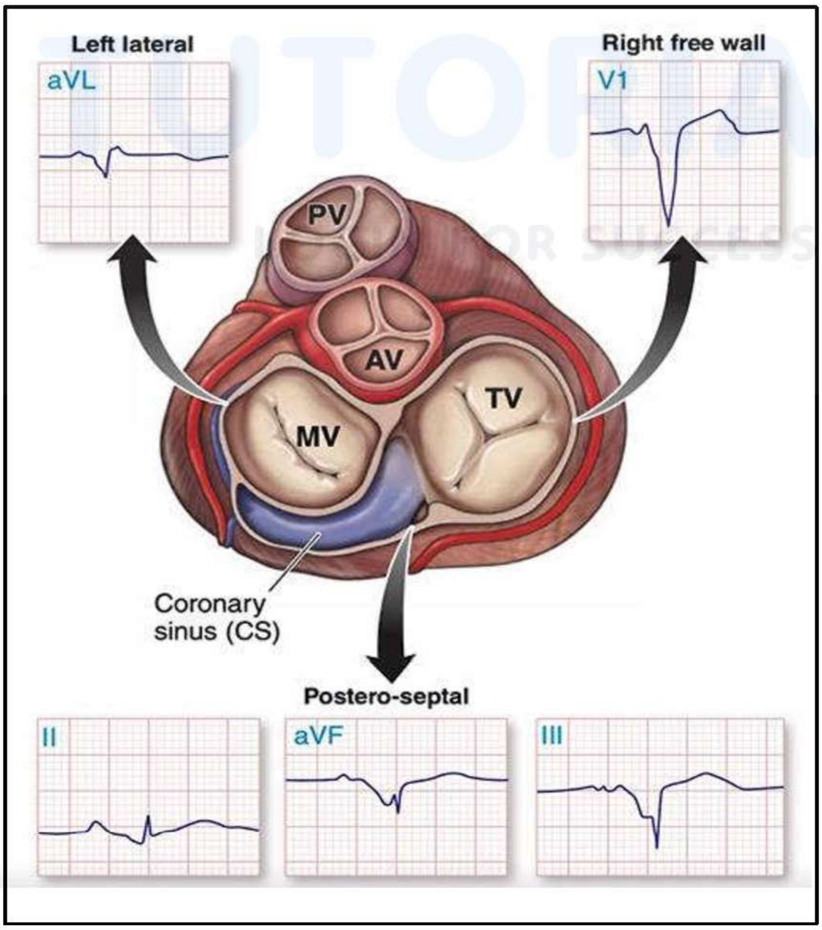
↓↓

Pre – excitation

↓↓

- Short PR interval <120 ms
- Slurred initial portion of QRS – DELTA WAVE
- Prolonged QRS

- Exact morphology of QRS and PR interval depends on location of the accessory pathway



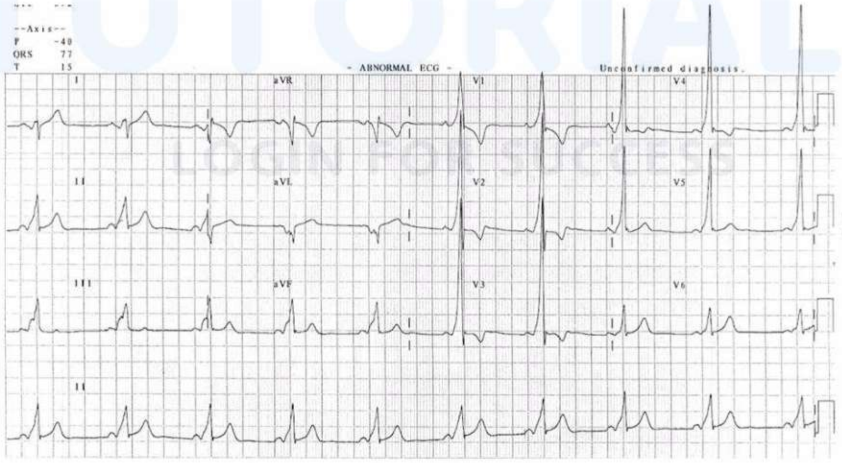
- Right sided accessory pathway
  - Pre – excitation of RV
  - LBBB in lead V_1
- Left sided accessory pathway
  - Pre- excitation of LV
  - RBBB in lead V_1

WPW Syndrome

- Characterized by pre – excited QRS during sinus rhythm
- Episodes of PSVT

WPW Pattern

- Patient with pre – excitation in ECG
- Absence of symptomatic arrhythmices
  - WPW type A pattern



WPW Type A pattern

- Short PR interval
- Broad QRS
- Delta wave

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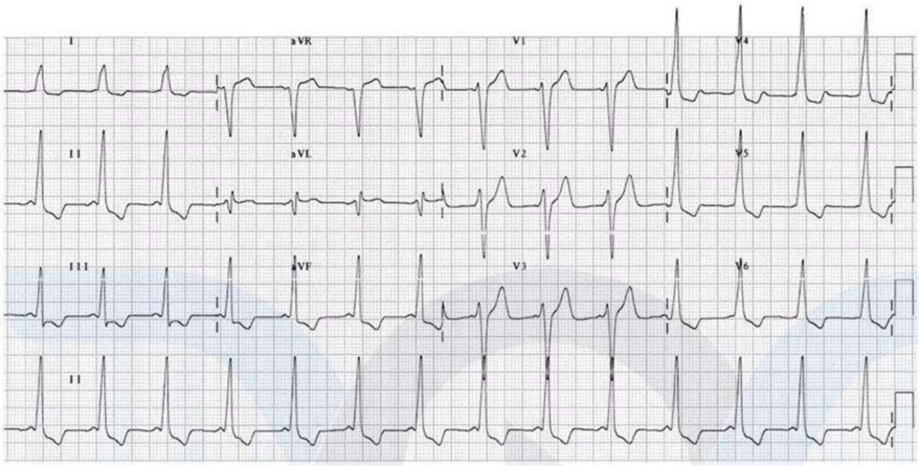
- Dominant R in V_1 → presence of lift sided accessory pathway
- Lead avL – negative delta wave, k/a Pseudo infarction pattern



WPW type B pattern

- Sinus rhythm
- Short PR interval
- Dominant S wave → presence of right sided AP
- Tall R wave and inverted T waves in V_4, V_5, V_6

  ↓↓

  Mimics LVH

Concealed pathways 00:22:01

- Impulse propagation occurs only in retrograde direction

AVRT 00:23:10

- AV – re entrant tachycardia
- AV – reciprocating tachycardia

- Re – entrant tachycardia
- Anatomical circuit → normal AV conduction system

  → AV accessory pathway
- Most common tachycardia – orthodromic AV re – entry tachycardia

Orthodromic AV-re-entry 00:25:40

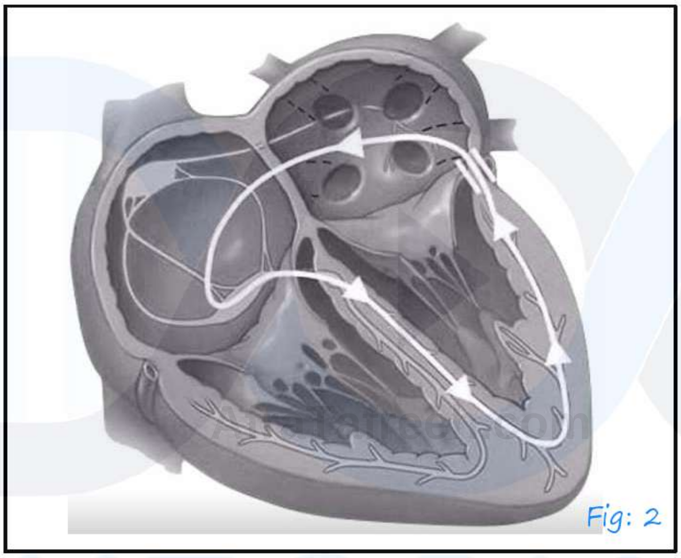


Fig: 2

- Impulse originates from atrium
- Impulse is conducted via AV node, his purkinje system → anterograde connection
- Retrograde connection via accessory pathway
- This will create a loop and is called orthodromic AV re-entry
- Orthodromic AV re-entry is characterized by narrow QRS

  →No pre-excitation

RP interval shorter than PR interval

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P wave → follows QRS

P wave morphology will be based on location of the accessory pathway

- Extremely slow retrograde propagation of impulse

↓↓

Results in tachycardia with long RP interval

Eg: Septal accessory pathway

- Referred to as permanent junctional reciprocating tachycardia → PJRT
- Can lead to tachycardia induced cardiomyopathy

Pre-excited tachycardia 00:31:56

- Ventricular activation is via accessory pathway antegrade conduction
- Most common mechanism – antidromic AV – re-entry
- Characterized by →
  - wide QRS complex
  - Similar to monomorphic VT
- By stander AP conduction → rapid conduction of impulses
- Pre – excited AF: - accessory pathway allowing propagation of impulse in addition to normal his bundle puriciujes

↓

If you give AV nodal blocking agents in such condition

↓

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Entire condition occurs through the accessory pathway and this can actually increase ventricular rate.

ECG findings → Orthodromic AVRT 00:37:31

- Ventricular rate: - 150 – 250 /min
- Narrow QRS
- RP interval < than ½ of RR interval

ECG findings → antidromic AVRT 00:38:47

- Ventricular rate: - 150 – 250 /min
- Wide QRS
- RP interval > ½ of RP interval
  - Wide complex tachycardia

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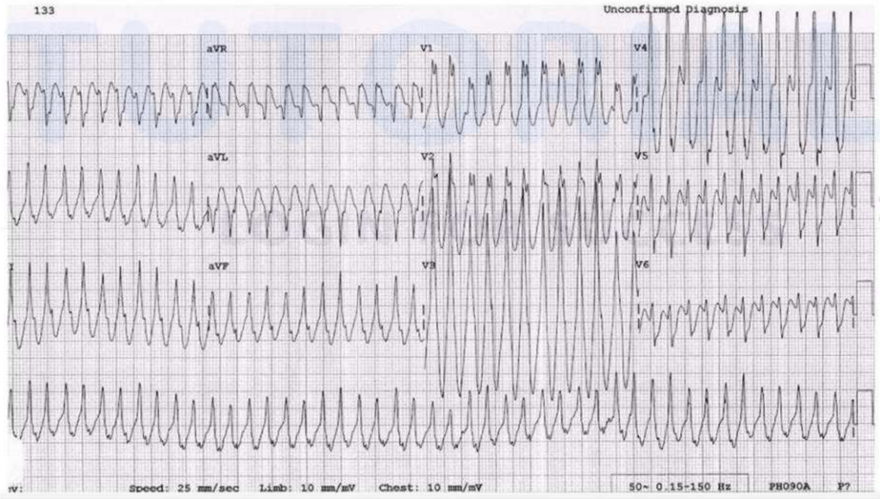

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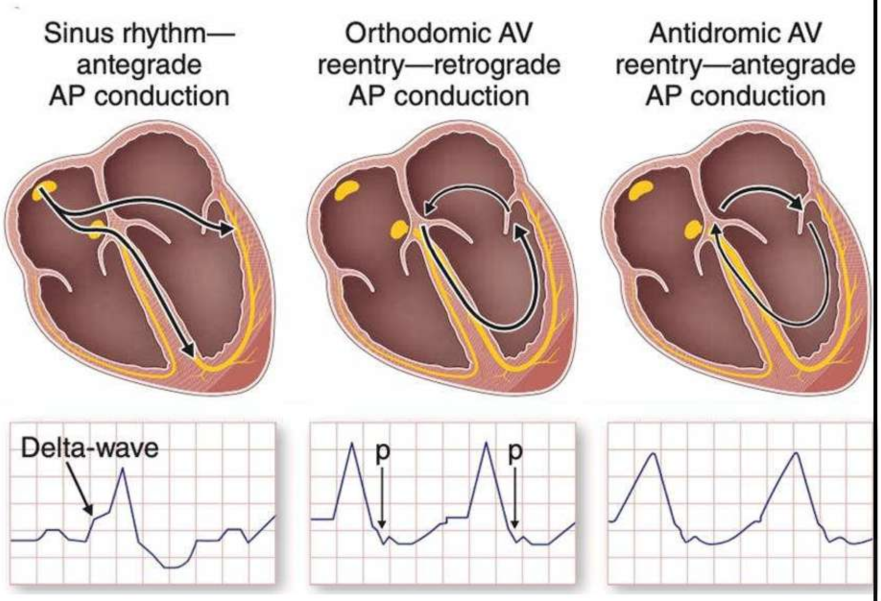

Fig: 3

Treatment of AVRT 00:41:53

Orthodromic AV reentrant tachycardia	
Acute termination	**Unstable patients:** Synchronized cardioversion **Stable patients:** • **First line:** Vagal maneuvers • **Second line:** IV adenosine • **Third line:** IV verapamil or IV diltiazem • Other therapies: IV procainamide or IV beta blocker; synchronized cardioversion other therapies are ineffective or not feasible
Chronic prevention	**First line:** Catheter ablation of the accessor pathway

	Second line: Oral flecainide or propafenone the absence of structural or ischemic heart disease **Third line:** Oral IA antiarrhythmic agent or oral amiodarone

Antidromic AV reentrant tachycardia	
Acute termination	**Unstable patients:** Synchronized cardioversion **Stable patients (if CERTAIN of the diagnosis):** Same progression of therapies as acute termination of orthodromic AVRT **Stable patients (if NOT certain of the diagnosis):** IV procainamide, synchronized cardioversion if procainamide is ineffective or not available
Chronic prevention	**First line:** Catheter ablation of the accessory pathway **Second line:** Oral flecainide or propafenone in the absence of structural or ischemic heart disease **Other therapies:** Oral IA antiarrhythmic agent OR oral amiodarone

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Pre-excited atrial fibrillation	
Acute termination	**Unstable patients:** Synchronized cardioversion **Stable patients (if CERTAIN of the diagnosis):** • First line: IV ibutilde or IV procainamide **Other therapies:** IC antiarrhythmic agent or dofetilide; synchronized cardioversion if other therapies are ineffective or not available.
Chronic prevention	**First line:** Catheter ablation of the accessory pathway **Second line:** Oral flecainide or propafenone in the absence of structural or ischemic heart disease **Other therapies:** Oral IA antiarrhythmic agent OR oral amiodarone

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INTRODUCTION

- Most complex valve - Mitral Valve
- 3 condition that can affect mitral valve
  i. Obstruction/stenosis of valve – least common
  ii. Leakage/regurgitation of valve
  iii. Prolapse of valve → Most common

Structure and function of mitral valve

- Mitral valve consists of 2 leaflets
  - Anterior
  - Posterior
- These leaflets are arranged to form a ring
- Anterior and posterior mitral valve have complex supporting structures
  ↓
  Strings on a parachute

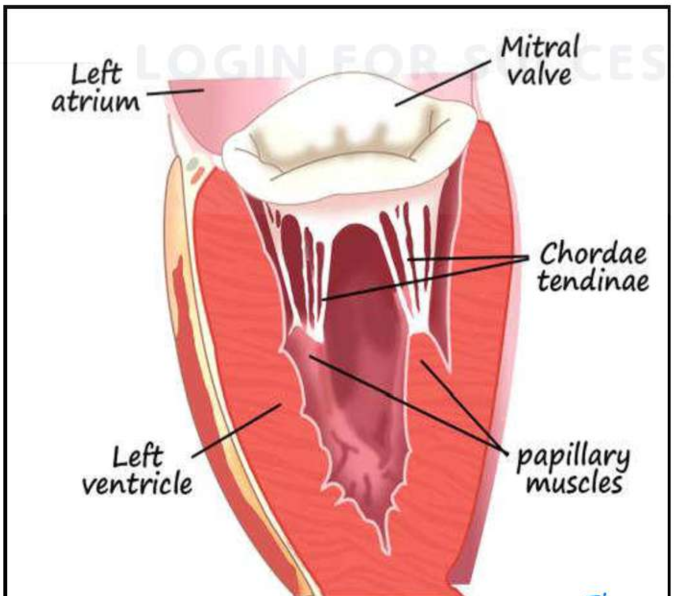

Fig: 1

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Function of mitral valve 00: 05:28

- Gateway between Left atrium and Right ventricle
- During diastole → LV relaxed state

→ Mitral valve opens

↓

Blood from LA → LV

- During systole → Valve closes

↓

Prevents backflow

Heart in Diastole 00:08:40

- Normal individuals: - LA→ LV blood flows

Fig: 2

- Mitral stenosis: - valve has characteristic "Domed appearance"

→ restricted opening of valve

→ thickened valve

→ LA will be enlarged

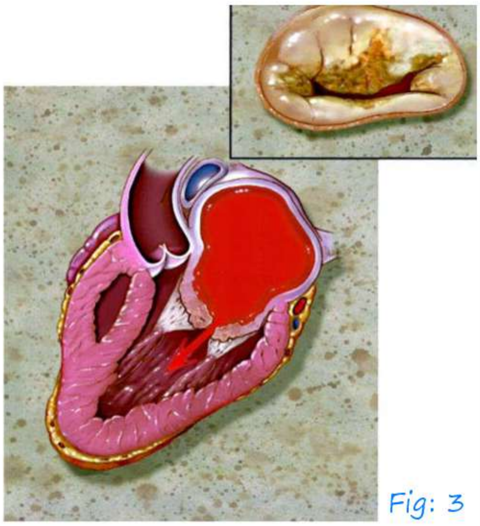

Fig: 3

Heart in Systole 00: 12:09

- Normal individuals: - Closed valve

→ No leakage to LA

- Prolapses & MR: - Valve does not close completely

↓

Leaflets bulges to LA

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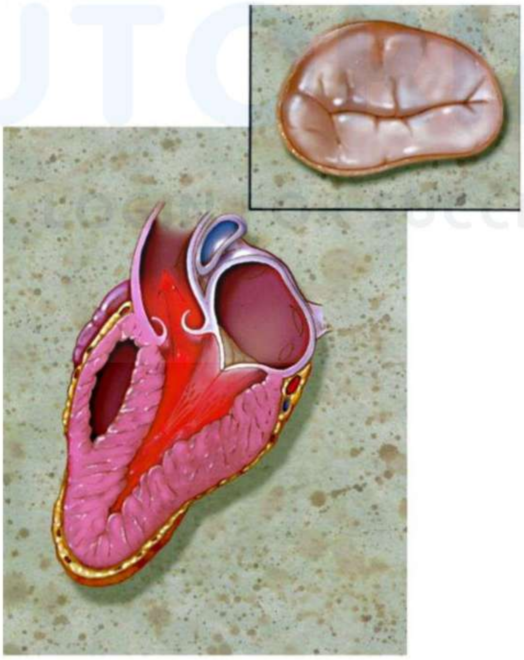
→ Enlarged LV as a result of chronic MR



Closed Mitral Valve

Fig: 4

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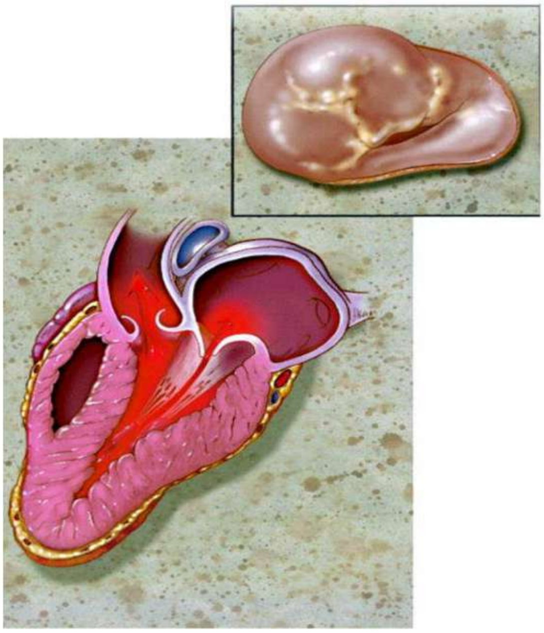

Damaged Mitral Valve

Fig: 5

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MITRAL STENOSIS

Etiology 00:00:47

- Most common cause – Rheumatic fever
- Pure/predominant MS – 40 % case of RHD
- 2/3rd of Rheumatic MS – females

Other etiologies associated MS

- Congenital mitral valve stenosis
- Mitral annular calcification extending to leaflets
- Cor Triatriatum
- Left atrial myxoma → stenosis
- RA, SLE
- Infective Endocarditis with large vegetations

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Pathology of Rheumatic MS 00:06:08

Cardinal features

- Thickening at leaflet edges
- Fusion of valve commissures
- Chorea tendinae shortening & fusion

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Acute Rheumatic Fever 00:08:08

- Inflammation and edema of valve leaflet
- Platelet fibrin thrombin along leaflet contact zones
- Subsequent scaring occurs
  - Valve deformity
  - Disruption of leaflet architecture

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- Neovascularization
- Increased collagen & tissue cellularity
- Funnel shaped/fish mouth shaped valve
- Calcification

Pathophysiology 00:12:36

Mitral valve orifice area

- Normal adults → 4-6 Sq.cm
- Around 2 Sq.cm– mild mitral stenosis
- < 1.5 Sq.cm– severe mitral stenosis

↓

Left atrioventricular pressure gradient of 20 mm HS

consequence of increase LA pressure

- Pulmonary venous HTN

↓

- Pulmonary capillary HTN

↓

Pulmonary arterial HTN → RV dilation & failure

↓

Secondary TR

Summary

- Elevated LA pressure → fundamental hemodynamic abnormality
- Increased pulmonary venous & capillary pressure

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Triggers 00:20:52

- Exercise
- Anemia
- Pregnancy
- Thyrotoxicosis
- Infections
- Atrial fibrillation

→ Increase the rate of blood flow across MV orifice
↓
Increase LA pressure

→ Decrease in diastolic filling time
↓
Decrease cardiac output

- Majority of manifestations of mitral stenosis is due to higher transmitral gradient
  ↓
  Inadequate LV filling

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AF in MS why? 00:24:21

- Left atrial dilatation
- Fibrosis of LA wall
- Disorganization of atrial muscle fibres
- Once AF is established
  ↓
  Hemodynamic detoriation
  Why? – Impaired LA contractility
  ↓ CO
  AF can predispose to thrombus formation

Clinical presentation 00:27:20

- Dyspnea → a/w cough
- Fatigue
- Decreased exercise tolerance

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- Vital capacity is reduced
  - Engorged pulmonary vessels
  - Interstitial edema
- Once a critical stenosis develops → orthopnea
  → Pulmonary edema
- Increase in pulmonary vascular resistance
  ↓
  RV dysfunction → Edema
  → hepatomegaly
  → Ascites
  → Hydrothorax
- Hemoptysis → due to rupture of thin-walled dilated bronchial veins
  ↓
  Increase LA pressure
- Acute pulmonary edema → rupture of pulmonary alveolar capillaries
  → Results in pink frothy sputum
- Pulmonary infarction → can lead to hemoptysis
- Occasional chest pain → 15% of MS patients
  → may due to severe RV HTN
  → coronary embolization
  → co-existent coronary atherosclerosis
- Palpitations & embolic events → MS + AF

- Rare manifestations → compression of Left recurrent laryngeal nerve

  ↓

  Hoarseness of voice

  ↓

  Ortner syndrome

Examination Findings 00:39:13

- Pulse volume → Normal

  ↓

- low volume pulse - severe MS
  - PAH
  - cardiac failure
- Atrial fibrillation – irregularly irregular pulse
- BP → usually normal

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- Narrow pulse pressure seen in : cardiac failure, PAH
- JVP → may be normal

  In Sinus Rhythm → PAH + RVH: - prominent a wave

  When RV failure + TR → Raised JVP

  AF: - Absent a wave
- Apex beat → Tapping apex

  → Diastolic thrill
- PAH → Left parasternal beave

  Palpable P2

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Auscultatory features → loud S1

→ mid-diastolic murmur

→ opening snap

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- Loud S1: - why? wide closing excursion of leaflets
- Marked calcification & thickening → reduction in loudness of S1
- Other causes of soft S1 in MS → associated MR
  → associated AR, AS
- Loudness of S1 → related to mobility of valve leaflets
  ↓
  Not related to severity

Mid diastolic murmur

- Diastolic low pitched, rumbling murmur
- Best heard @ apex
- Best heard with bell of stethoscope
- Patient should be in Left lateral recumbent position (ideal position)
- Duration of MDM → severity of MS
- Absent MDM → severe silent MS
  → severe cardiac failure
  → emphysema
  → obesity
- Pre-systolic accentuation of MDM → increase in loudness of murmur just before systole
  ↓
  Occurs because of atrial contraction → Rheumatic MS
- AF → absent presystolic accentuations

Other causes of MDM:

- Carey Coombs murmur → Acute RF
- Increased flow across non stenotic mitral valve

  ↓

  Large VSD

  PDA

  severe MR
- Increased flow across non stenotic trianryuoid valve

  ↓

  - Large ASD
  - Severe TR
- Severe AR → Austin flint murmur
- Atrial myxoma

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Opening snap of mitral valve

- Occurs because of sudden tensing of valve leaflets
- After the valve clerps has completed their opening excursion
- Best audible at apex
- Best audible using diaphragm

Opening snap Vs S2

- OS occur later
- OS- loudest at apex
- S2 – best heard at base

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- opening snap + → mitral valve is not significantly rigid & calcified
- OS has loud S1
- Mitral OS follows A2 by a gap of 0.04-0.12 seconds
- A2 – OS interval varies inversely with LA pressure
- Shorter A2 - OS interval → severe MS

Other auscultatory features

- When pulmonary arterial pressure increases → loud P2
- PAP increase → Narrow split S2
  - Because there is reduced compliance of pulmonary vascular bed
  - Earlier pulmonic valve closure
- Late stages → single S2
- Non vascular pulmonary ejection sound--? Due to dilation of pulmonary artery

  ↓

  Diminish during inspiration
- PSM → functional TR
  - → louder during inspiration
  - → diminished during expiration

  (louder during inspiration / diminished during expiration: carvallo's sign)
- Graham steel murmur of pulmonary regurgitation

  ↓
  - Hight pitched diastolic decrescendo blowing murmur

- Dilation of pulmonary valve ring

- S4→ RVH+ 2° PAH
- LVS₃ – usually absent in MS unless coexisting AR or MR
- Severe chronic MS → mitral facies
  - 1.Pinkish purple patches on cheeks
  - 2.low CO_2 systemic Vaso constriction

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EVALUATION AND MANAGEMENT OF MS

Evaluation 00:00:27

- ECG Changes: -
  - Mild (Most common) : - Relatively insensitive
  - Moderate to severe MS: - ECG Changes significant MS and in sinus rhythm

↓↓

LA enlargement – 90% cases

  - Long standing MS: - Atrial fibrillation
  - MS and Pulmonary HTN: - RVH and right axis deviation
- CXR Findings: -

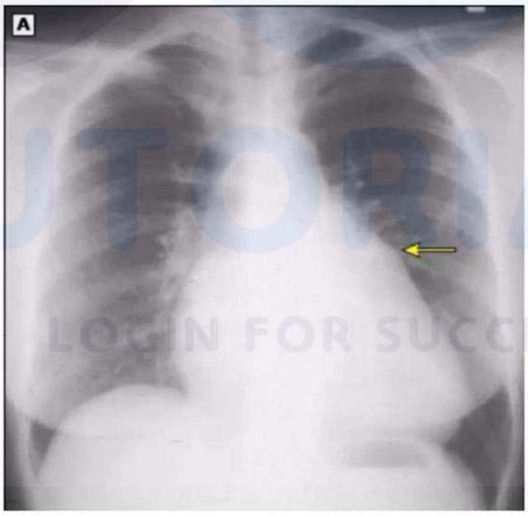

Fig: 1

  - Early radiological findings: - Straightening of upper left border of heart border
  - Hemodynamically significant MS: - LA enlargement

- Extreme LA enlargement: - Less likely unless there is co-existent MR
- Other radiological findings
  - Prominence of main pulmonary artery
  - Dilatation of upper lobe pulmonary veins (Cephalization of pulmonary vasculature)
  - Posterior displacement of esophagus by enlarged LA
  - Kerly lines
    - Thickened interlobular septa
    - Interstitial edema development → kerly B lines

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↓

- Short, horizontal lines
- Seen at costophrenic angles
- Prominent in lower and middle lung fields
- Resting mean LA pressure – 20mmHs severe

- Long standing MS – kerly A lines → dense
  - Straight, lines, can be approximately 4 cm in length
  - Run from periphery towards hilum

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- Kerly C lines
  - Reticular apacites at the lung base
  - Represent end on view of kerly B lines

Severe MS with pulmonary HTN

- Enlargement of pulmonary artery
- RV enlargement
- RA enlargement

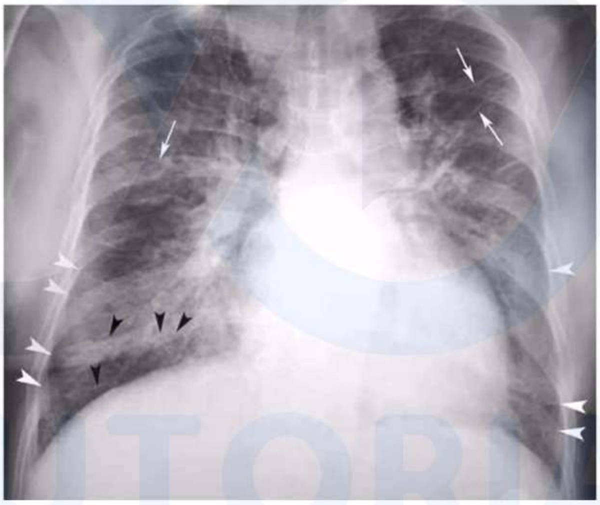

Fig: 2

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Double density sign

- Double atria sign

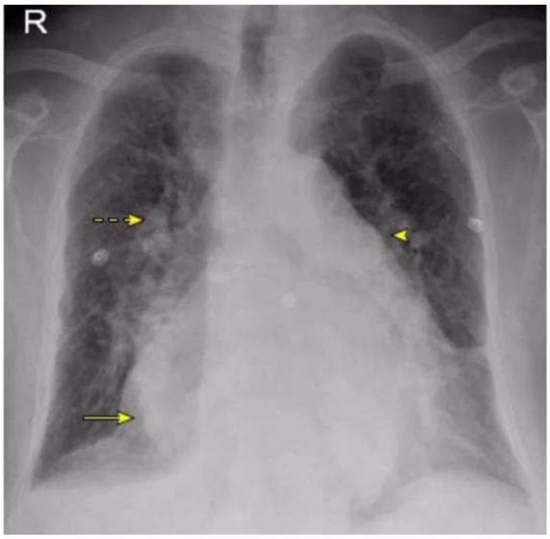

Fig: 3

- As the disease progresses, there may be elevation of left main bronchus and also splaying of carina
  - Lateral radiograph after radio-opaque contrast

    ↓↓

    Compression of lower esophgus by the enlarged LA

Fig: 4

Echocardiography

- All patients suspecting MS at presentation
- Re- evaluation → new symptoms and signs
- To monitor disease progression
- TTE with color flow and spectral doppler
  - Identify transvalvular pressure gradients
  - Chamber dimensions
  - Mitral inflow velocity during diastolic filling
  - Associated MR
  - Valve architecture (distortion, calcification, mobility)

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- Anatomic suitability for percutaneous balloon mitral valvuloplasty

TEE

- Trans erophageal echo
- Superior image
- To rule out LA thrombus

Cardiac catheterization

- Routine cardiac cathelerization – not necessary
- Monitoring purpose prior, during and after PBMV
- Some role when we have discrepancy
- Measure LA and LV pressure
- Assess mean trans-valvular pressure gradient
- Measuring trans-mitral volume flow rate
- Valve area measurement – Gorlin formula

Management 00:27:27

2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease

Developed in collaboration with and endorsed by the American Association for Thoracic Surgery, American Society of Echocardiography, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons

Diagnostic Testing: Initial Diagnosis of Rheumatic MS

COR	LOE	Recommendations
1	B-NR	1. In patients with signs or symptoms of rheumatic MS, TTE is indicated to establish the diagnosis, quantify hemodynamic severity, assess concomitant valvular lesions, and demonstrate valve morphology (to determine suitability for mitral commissurotomy).
1	C-LD	2. In patients considered for percutaneous mitral balloon commissurotomy (PMBC), TEE should be performed to assess the presence or absence of LA thrombus and to evaluate the severity of MR.

Diagnostic Testing: Exercise Testing in Patients with Rheumatic MS

COR	LOE	Recommendations
1	C-LD	1. In patients with rheumatic MS and a discrepancy between resting echocardiographic findings and clinical symptoms, exercise testing with

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		Doppler or invasive hemodynamicassessment is recommended to evaluate symptomatic response, exercise capacity, and the response of the mean mitral gradient and pulmonary artery pressure.

Stages of Mitral Stenosis (MS)					
Stag	Definition	Valve anatomy	Valve hemodynamics	Hemodynamic consequences	Symptoms
A	At risk for MS	Mild valve doming during diastole	Normal transmitral flow velocity	None	None
B	Progressive MS	Rheumatic valve changes with commissural fusion and diastolic	Increased transmitral flow velocities MVA>1.5 cm^2 Diastolic pressure	Mild to moderate LA enlargement Normal pulmonary pressure at rest	None

		doming of mitral valve leaflets Planimetered MVA >1.5 cm^2	half-time <150 msec		
C	Asymptomatic severe MS	Rheumatic valve changes with commissural fusion and diastolic doming of mitral valve leaflets Planimetered MVA	MVA ≤1.5 cm^2 (MVA ≤1 cm with very severe MS) Diastolic pressure half-time ≥150 msec (Diastolic pressure half-time	Severe LA enlargement Elevated PASP >30 mm Hg	None

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		≤1.5 cm^2 (MVA ≤1 cm^2 with very severe MS)	≥220 msec with very severe MS)		
D	Symptomatic severe MS	Rheumatic valve changes with commissural fusion and diastolic doming of mitral valve leaflets Planimetered MVA ≤1.5 cm^2	MVA ≤1.5 cm^2 (MVA ≤1 cm^2 with very severe MS) Diastolic pressure half-time ≥150 msec (Diastolic pressure half-time ≥220	Severe LA enlargement Elevated PASP >30 mm Hg	Decreased exercise tolerance Exertional dyspnea

			msec with very severe MS)		

Medical management 00:34:00

1.Prevention of recurrent rheumatic fever

2.Prevent and treatment complications of MS

Secondary Prevention of Rheumatic Fever	
Antibiotics for Prevention	Dosage
Penicillin G benzathine	1.2 million U intramuscularly every 4 week
Penicillin V potassium	200 mg orally twice daily
Sulfadiazine	1 g orally once daily
Macrolide or azalide antibiotic (for patients allergic to penicillin and sulfadiazine)†	Varies

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Duration of Secondary Prophylaxis for Rheumatic Fever	
Type	Duration After Last Attack*
Rheumatic fever with carditis and residual heart disease (persistent VHD†)	10 y or until patient is 40 y of age (whichever is longer)
Rheumatic fever with carditis but no residual heart disease (no valvular disease)	10 y or until patient is 21 y of age (whichever is longer)
Rheumatic fever without carditis	5 y or until patient is 21 y of age (whichever is longer)

Indications for anticoagulation

1) Atrial fibrillation
2) Any prior embolic event
3) LA thrombus

- Warfarin – drug given

Mitral valvotomy

- Percutaneous mitral balloon valvuloplasty (PMBV)
- Surgical valvotomy
  - Closed mitral valvotomy

- Open mitral valvotomy
- Mitral valve replacement

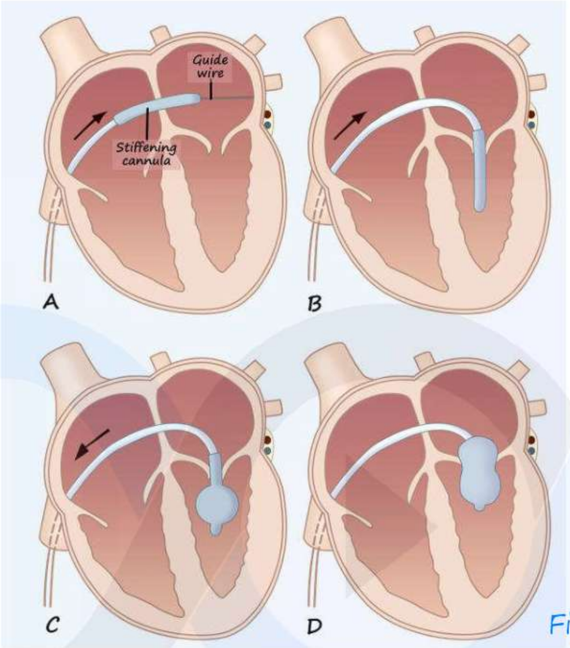

Fig: 5

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Inoue balloon technique

↓↓

Transseptal puncture between lift atrium and right atrium

↓↓

Inflated across mitral valve

Indications for PMBV

- Symptomatic patients with severe rhematic MS (Stage D)
- Favorable valve morphology
- Less than moderate MR → sellar's criteria (0-4+) (<2+)
- Absence of LA thrombus

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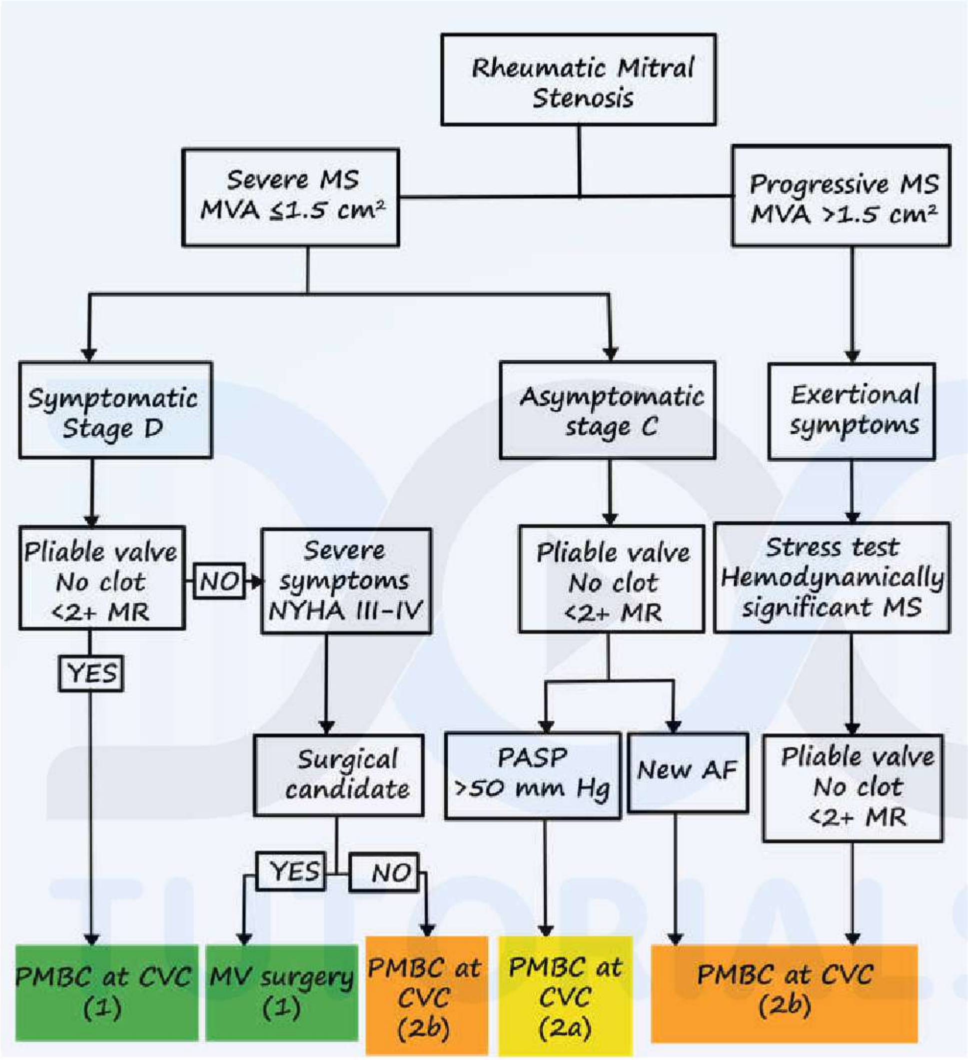
Indications for surgery

- Not a candidate for PMBC
- Failed previous PMBC



MITRAL REGURITATION

- MR occurs because of dysfunctional mitral valve apparatus Which consists of
  - Mitral leaflets- anterior and posterior
  - Mitral annulus- anterior and posterior
  - Chordae tendineae
  - Papillary muscles – lateral and medial
  - Supporting wall of left ventricle & a part of left atrium

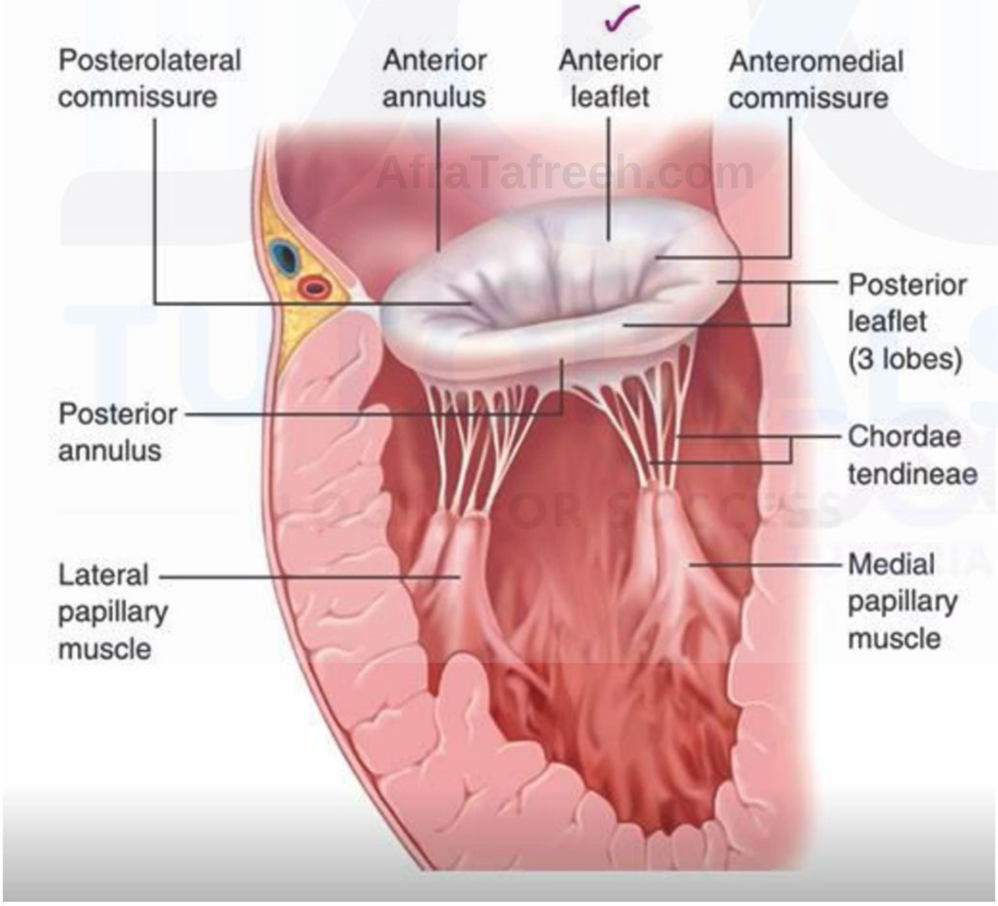


Fig: 1

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- Mitral leaflets are connected to left atrium by annulus and left ventricle by chordae tendineae and papillary muscle

Aetiology of MR 00:4:39

- Acute MR
  - Infective Endocarditis
  - Acute myocardial Infarction
  - Blunt trauma
  - Chordal rupture /leaflets flail (MVP, IE)
- In Acute MI, posteromedial papillary muscle is involved
- Note: posteromedial papillary muscle is only supplied by right coronary artery whereas anterolateral is supplied by both left anterior descending and anterior circumflex

Chronic MR

primary	Secondary
Organic/Degenerative	Functional
Leaflets / chordae tendineae dysfunction	LV remodelling & mitral annular dilation

Etiologies of chronic MR

Primary (Affecting leaflets, chordae)	Secondary (Leaflets, chordae are innocent bystanders)
• Myxomatous (Mitral Valve Prolapse, Barlow's, former fruste) • Rheumatic Fever (rigidity, retraction of valve cusps, fusion, shortening of chordae) • IE (Healed) • Congenital (Endocardial cushion defect, Cleft anterior Mitral Valve Leaflet) • Radiation	• Ischemic cardiomyopathy - Ventricular remodelling • Dilated cardiomyopathy • HOCM (with SAM) - Dynamic MR due to Systolic Antenor Motion of anterior valve leaflet into narrowed LV outflow tract • Atrial Fibrillation with LA enlargement and annular dilation (atrial functional MR)

MAC (Mitral Annular Calcification)

- Seen in Older adults
- mild-moderate severity

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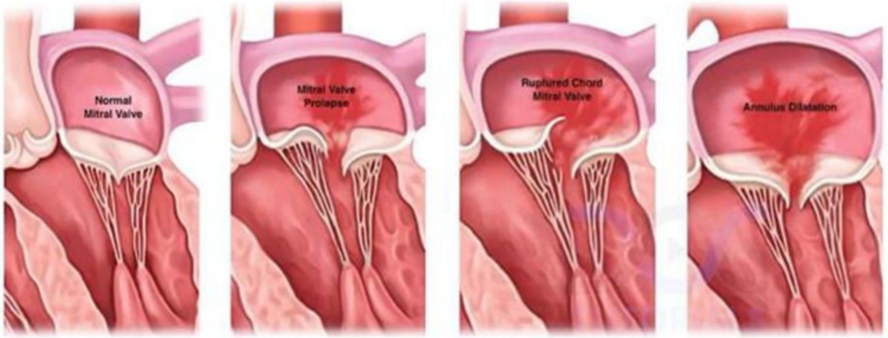

Fig: 2

Hemodynamic changes associated with MR

00:16:55

Acute MR

- During the LV Systole, Mitral Valve leaflet bulges into the left atrium
  - Forward Flow from LV →aorta
  - Backward Flow from LV to LA
    depends on I) size of the regurgitant orifice
    II) (LV-LA) Pressure Gradient
  - LA Volume and Pressure ↑↑

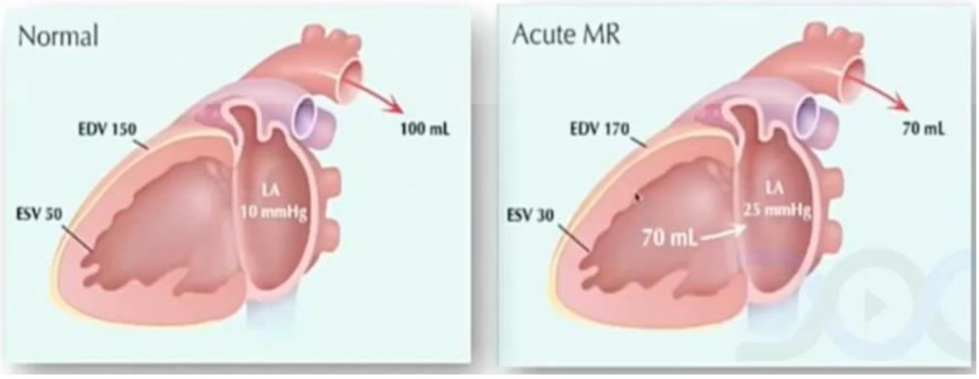

Fig: 3

LVEDP –↑↑ During diastole (Left Ventricular End Diastolic Pressure)

- Volume overload in LA and LV
- According to Frank Starling's law the force of contraction is directly proportional to EDV
- Total Stroke Volume (forward and Backward Flow) increases
- In acute MR, Pulmonary edema is seen
- In acute MR, Contractility is Normal but cardiac failure with reduced Cardia output

Chronic MR

- Chronic compensated MR: –Body has got two goals
  - Improve Forward Cardiac output
  - Reduce Pulmonary congestion
- Major change in evolution of acute MR to chronic MR is **change in LV**
- In acute MR – Normal sized but hyperkinetic LV
- In chronic MR – LV is converted to large compliant chamber
- In LV rearrangement of myocardial fibres
- LA dilatation → Compliance of LA ↑
  → LA Pressure ↓
- That's why PCWP (Pulmonary Capillary Wedge Pressure) in Acute MR is high than in Chronic MR
- LA pressure is higher in acute MR than chronic MR but Pressure difference is higher in chronic MR

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- Regurgitant Fraction in Chronic MR ↑↑ in comparison to acute MR
- In chronic MR, because of Hemodynamic compensation → there is reduced pulmonary oedema and congestion; aka compensatory dilatation of LV and LA are able to accommodate volume overload at lower pressures and hence pulmonary congestion is reduced

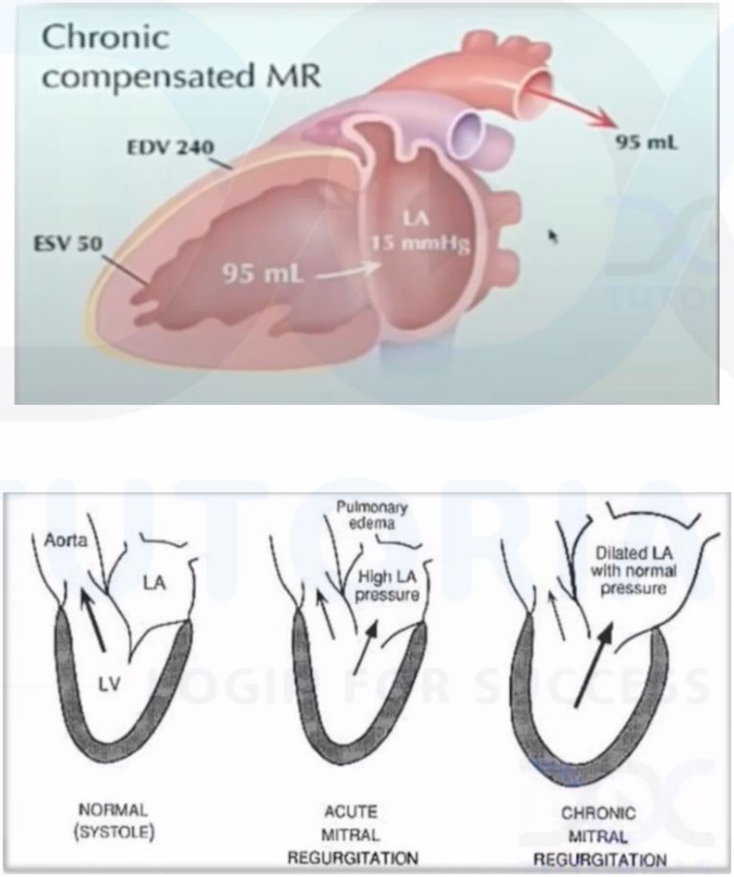

Fig: 4

Chronic decompensated MR

- In chronic MR, there might be LV dysfunction, Heart Failure, Atrial Fibrillation→ chronic Decompensated MR

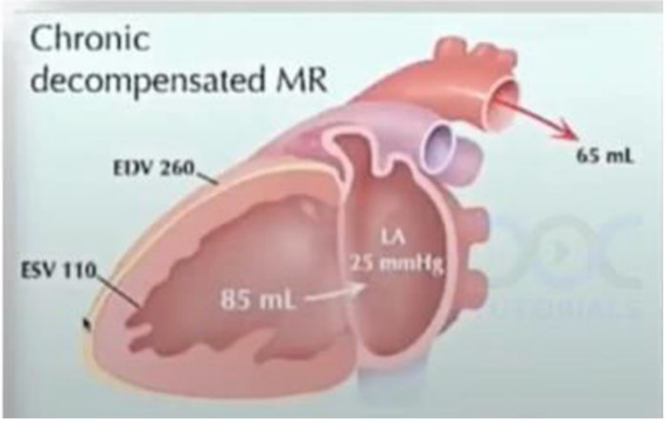

Fig: 5

- ↓ Ejection Fraction
- ↓ ESV (End systolic volume) → ↑ EDV&EDP
- Forward stroke volume - ↓
- LA pressure ↑ and there is pulmonary congestion and oedema

- MR begets MR

  As MR progresses there is LV dilatation

  ↑

  ↑ annulus size

  ↑

  ↑ Regurgitation

Clinical Features 00:39:11

- Symptom depends on:
  - Stage
  - Severity
  - Rate of Progression
  - Pulmonary artery pressure
  - Arrhythmias like atrial fibrillation

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- Associated cardiac conditions

- Chronic mild moderated isolated MR → asymptomatic
- MVP-MR → majority are asymptomatic
- Chronic severe MR → Fatigue
  → Exertional Dyspnoea
  → Orthopnoea
  } Acute Pulmonary Oedema
- Acute MR
- Chronic decompensated MR
- Acute MR or advanced severe mitral Regurgitation → may also have features of right sided heart failure
  → congestive Hepatomegaly
  → oedema
  → ascites
- Symptoms of Underlying cause of MR like IE, SLE, Marfan's syndrome,

Examination Finding 00:47:02

Arterial Pulse

- Chronic MR: Normal because LV Ejection Time and Forward Stroke volume is relatively Normal.
  - Acute MR
  - Chronic decompressed MR
  } Rapid reduction in the volume of forward flow in late systole, Decrease in Ejection

↓

Bounding Pulse.

– Pulse Pressure in AR is High, but PP in MR is Normal

- Blood Pressure in MR- normal
- Apex Beat → Brisk and hyperdynamic because LV apex is displaced to left
- Systolic Thrill → over apex

Auscultatory findings

S_1

- In Significant MR- S1 is Soft (especially if RHD MR)
- Normal S1 is possible if
  - Mild MR
  - MVP MR
  - MR due to Papillary Muscle dysfunction
- S_1 is buried Pansystolic Murmur of MR.

S_2

- Significant MR- Wide Split of S_2 due to Premature closure of aortic valve
- Severe Pulmonary Hypertension → P_2 is loud.

S_3

- Low Pitched S_3
- In MR, S_3 not a sign of Heart Failure

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- if S3 heard then this MR is severe, Significant MS is unlikely

Pan Systolic Murmur

- at least Grade III/VI
- Best heard with Diaphragm of Stethoscope which is placed over apex - Patient should be ideally in left lateral Position

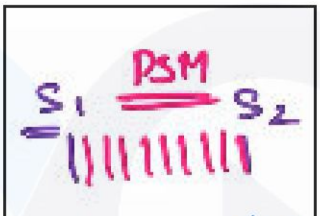

Fig: 6

- Just after S_1, LV Pressure > LA Pressure
- Murmur of MR is Holosystolic Murmur
- Nature is Blowing High Pitched murmur

- If Antenor mitral leaflet is involved
  - posteriorly directed regurgitant jet
  - Radiation to Left axilla and Left intrascapular area
- Posterior mitral leaflet involved
  - Anteriorly directed jet
  - Radiation to the aortic area and Sternum and No radiation to carotids
- It may be confused with ESM (Ejection Systolic Murmur) of AS - it radiates to carotids
- LV Volume ↑

- Heart failure
- Supine position
- ↑ arterial pressure → squatting
  → Isometric handgrip

} Louder pan-systolic Murmur

- ↓ venous return Standing Valsalva → Decreased intensity of PSM
- NO relation between Intensity of PSM and severity of MR
- Acute severe MR- Decrescendo murmur stops in mid to late systole

- Ruptured chordae tendineae → cooing /sea gull quality
  - Seen in MR SBE (subacute Bacterial Endocarditis)
  - Sea gull/cooing dove murmur

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Silent MR

- when severe MR is caused by
- LV dilation
- Acute MI
- marked emphysema
- Marked emphysema
- Obesity
- Prosthetic Valve

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- Apical MDM – Because ↑ flow through Valve in diastole which results in low pitch mid diastole rumbling murmur → Functional MS

Assessing Severity of MR 31:07:20

- Based on examination
  - Presence of apical MDM
  - LV S_3
  - Degree of LVH
  - Systolic thrill + PSM

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EVALUATION & MANAGEMENT OF MR

Lab evaluation: 00:00:25

1.ECG:

- Shows features of LA enlargement
  - Broadening of P-wave
  - Notching of P wave → P mitrale
- RA enlargement ± (depends on significant PAH)
- Eccentric LV Hypertrophy ±
- Chronic severe MR associated with Atrial fibrillation.

2.Echocardiography:

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- TTE (Transthoracic echo): Used to assess
  - Severity
  - Etiology
  - Hemodynamic consequences
- LA size increased
- LV size is normal initially→ progressive ventricular dilatation →reduced EF
- TEE (transesophageal echo) Provides greater anatomical details than TTE
- Doppler echocardiography: used to asses
  - Area/width of regurgitant jet
  - Regurgitant volume
  - Regurgitant fraction

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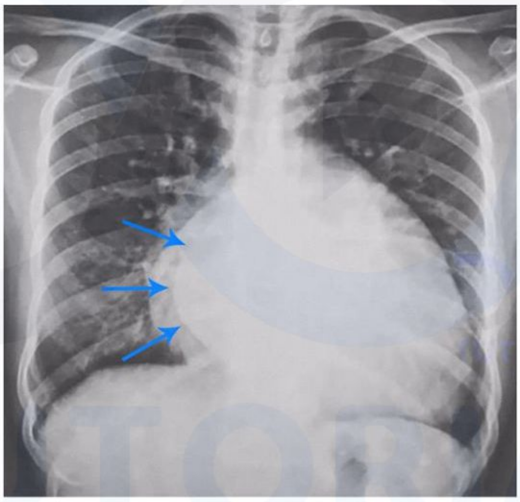
- ERO (Effective regurgitant orifice area)

3.Chest X-ray:

- Cardiomegaly due to LA & LV enlargement
- Globular shape of LV chamber
- LA enlargement
  - manifests as straightening left heart boarder
  - Double density sign / double border heart
  - Elevation of left main stem bronchus



Double density sign

Normal

MR

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- Long standing rheumatic MR + MS leads calcification of mitral annulus (Best seen in lateral view)

4.Cardiac MRI

- Not routinely used
- Used when echo findings & symptoms are discordant

5.Cardiac catheterization

Management 00:13:16

Based on chronicity

- Acute MR
- Chronic MR
  - Primary
  - secondary

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Chronic Primary MR: 00:14:22

- Divided into 4 stages based on valve anatomy, valve hemodynamics, Hemodynamic consequences, symptoms

Stage A: At risk of MR

Stage B: progressive MR

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Stage C: Asymptomatic severe MR

Stage D: Symptomatic severe MR

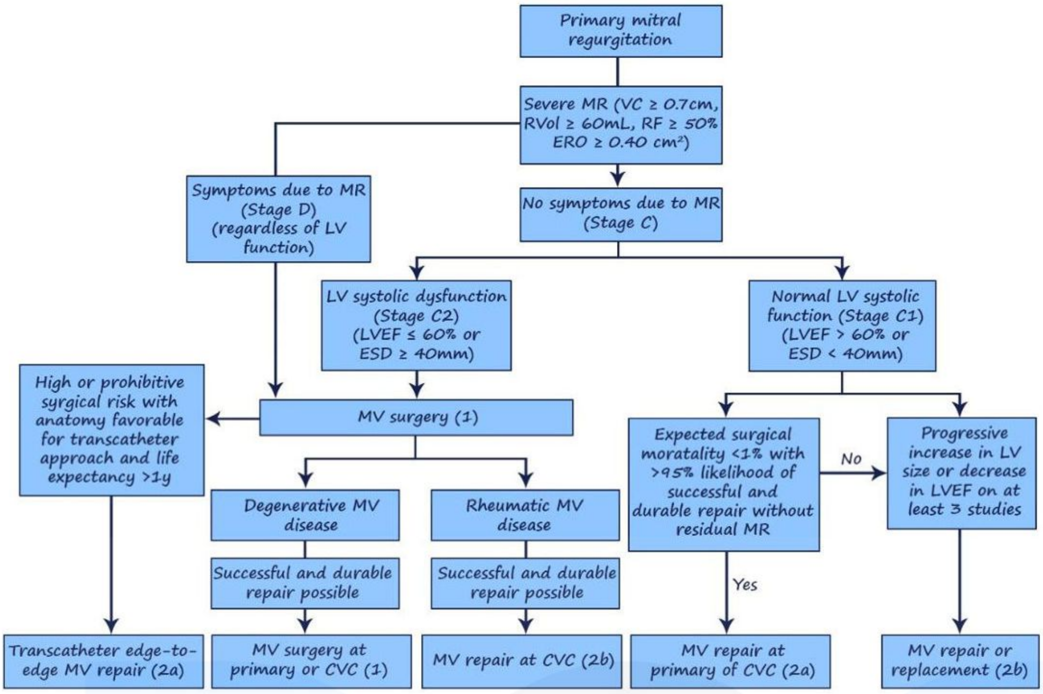
- Stage C is devided into C_1 & C_2 based on LV ejection fraction, LVESD (end systolic dimension)

Medical R_x:

- Limited role
- Antibiotic prophylaxis is not recommended except
  - Prosthetic valve replacement
  - History of infective endocarditis
- 2° preventions of RF

Surgical intervention:

- Based on risk, benefit ratio
- Valve repair is preferred than valve replacement due to less risk
- Valve replacement
  - Mechanical valve
  - Bioprosthetic valve
- **In stage C_2, stage D → surgical intervention**



Chronic secondary MR: 00:25:19

- It is also divided into 4 stages same as 1° MR

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Medical:

- Aggressive treatment for heart failure in patients with poor EF → GDMT (Guideline directed, B-blockers, ACE ⊖, Neprilysin ⊖, SGLT 2 ⊖, Biventricular pacing
- Role of antibiotic prophylaxis:
  - Not recommended
  - Exceptions: prosthetic valve repair, H/o infective endocarditis.

Surgical intervention:

Depends on symptoms, EF

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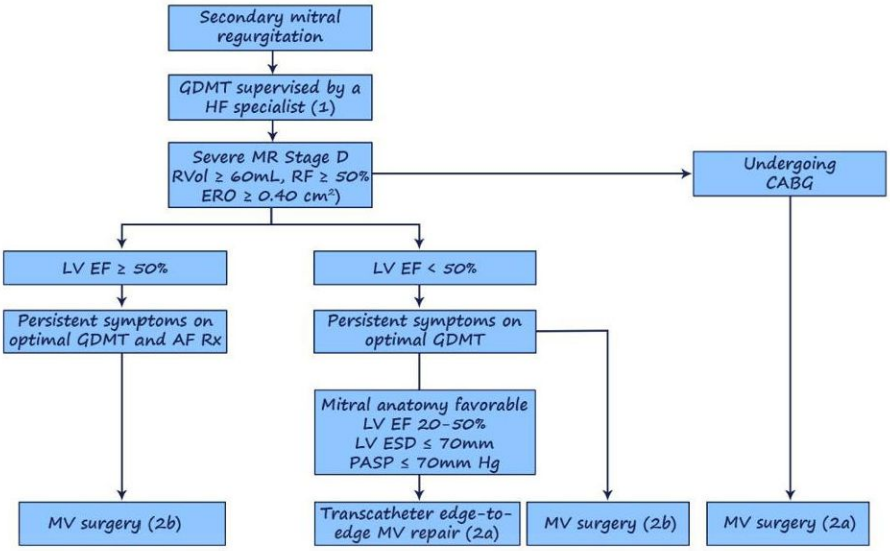

Acute MR: 00:29:43

- Symptomatic management & stabilization

  ↓

  Surgical intervention
- Medical P_x:
  - Diuretics
  - IV vasodilators like sodium nitroprusside to reduce afterload
- Mechanical support: IABP (Intra-Aortic balloon pump)

MITAL VALVE PROLAPSE (MVP)

- Site of pathology is mitral valve apparatus
- MVP is most common cause of primary MR

Pathology 00:01:34

- It is myxomatous degeneration of mitral leaflets
- Histology:
  - Proliferation of spongiosa
  - Increased accumulation of GAGs
  - Excess water content
- End result: excessive mitral leaflet tissue

↓

Thick elongated mitral valve,

It has tendency to prolapse

↓

Floppy mitral valve (posterior > Anterior)

- MVP with elongated chordal tendineae

& Reduced tensile strength of chordal tendineae

↓

Rupture

↓

Subsequent annular dilation

↓

Mitral regurgitation

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- MVP causes excessive stress on papillary muscles

  ↓

  Ischemia, disfunction of adjacent ventricular myocardium

  ↓

  Arrhythmias

Etiology 00:06:05

- Exact etiology still remains unknown
- Genetic basis – AD pattern
  - Alteration in production **type 3 collagen**
- Associated with connective tissue diseases:
  - Marfan's syndrome
  - Osteogenesis imperfecta
  - Ehler danlo's syndrome
- Rarely it associated with
  - Acute rheumatic fever
  - Ischemic heart disease
  - Cardiomyopathies
  - Ostium secundum ASD

Clinical features: 00:08:43

- Age group: 15-30 years
- Females > males
- Asymptomatic (majority)
- Diagnosed by auscultation

- Symptoms due to

MR

- Mostly mild MR
- Severe MR is uncommon

Arrhythmias

- VPC
- AF
- VT
- PSVT
- Presents with palpitation, syncope & atypical chest pain

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Auscultatory findings:

- **Non ejection click** either single / multiple, **mid to late systolic** in timing
- It is due to sudden tensing & snapping of elongated chordae tendineae & prolapsed leaflets during systole
- It is mobile click (timing of click vary based on alteration in left ventricular volume)

- Non ejection click followed by high pitched **mid to late systolic murmur** best heart at apex

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- Radiation of the mid-late systolic murmur:

  depends on involved leaflets

Posterior leaflet → Towards base of the heart

anterior leaflet → Towards axilla & back

Dynamic auscultation in MVP:

- Decreased LV volume in conditions like standing / Valsalva

  ↓

  Exaggeration of tendency to prolapse

  ↓

  Click & murmur moves close S_1

- Increases LV volume (squatting, Isometric exercise)

  ↓

  Decreases tendency to prolapse

  ↓

  Click & murmur moves close to S_2

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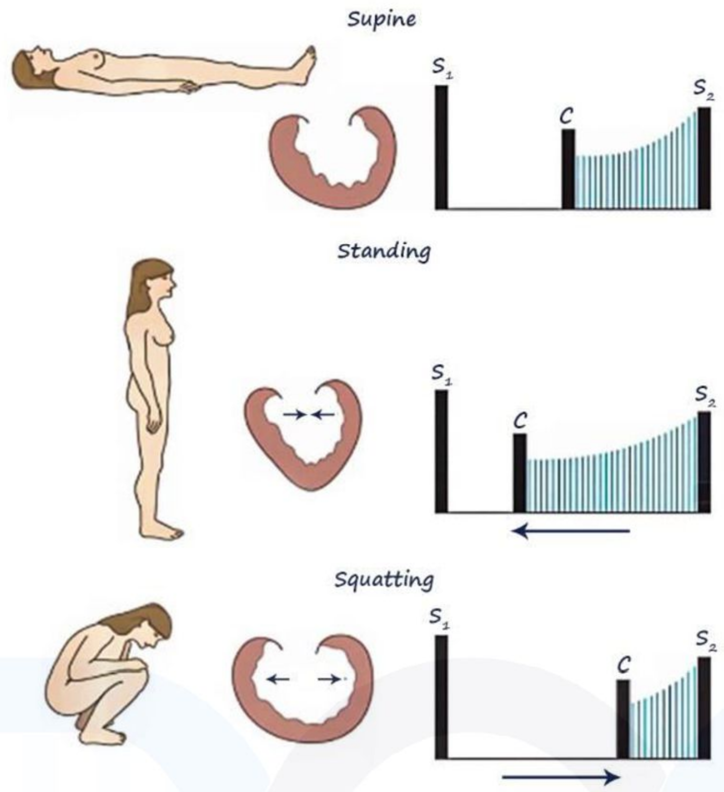

Lab evaluation 00:19:46

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ECG:

- Usually, normal
- Rarely VPC, T wave inversion seen.

Echo:

- **TTE** used to diagnose MVP
- To demonstrate prolapse of mitral valve leaflets
- To assess subvalvular structures, MR±, Hemodynamic consequences
- TEE for accurate anatomical details

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Management 00:21:42

Medical management:

- IE prophylaxis: useful in prior history of IE
- B-Blockers useful in pts with chest pain, & palpitations

Surgical management:

- Symptomatic severe MR
- Significant LV dysfunction

(Symptomatic severe MR and significant LV dysfunction → MV Repair)

- Repair >> replacement
- Pt of severe 1 MR due MVP with high surgical risk

↓

TEER (Transcatheter edge to edge repair)

Other terminologies for MVP:

- Systolic click murmur syndrome
- Barlow's syndrome
- Billowing mitral leaflet syndrome
- Floppy valve syndrome

INTRODUCTION AND ETIOPATHOGENESIS

- **AHA definition of Heart Failure:** - Complex clinical resulting from structural or functional impairment of ventricular filling or ejection of blood.
- **Congestive heart failure:** - not commonly used

Classification 00:04:23

i. Based on symptoms severity
ii. Based on disease progression
iii. Practical classification

i. Based on symptoms severity

- NYHA classification (New York Heart Association)

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Functional Capacity	Objective Assessment
Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

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- Annual mortality rate @ class II → 5-10%
  @ class IV 30-70%

ii. Based on disease progression

- ACC- AHA → Stage A→ D
  - Stage A: - at risk of developing heart failure
    No structural heart disease
    No signs & symptoms
  - Stage B: - there is structural heart disease
    No signs and symptoms
  - Stage C: - Refers to symptomatic patients
  - Stages D: - Individuals with advanced heart failures

Practical classification

a)

Chronic heart failure	Acute heart failure

b)

Prevented Heart Failure (LVEF ≥ 50 %) (Diastolic heart failure)	Hear Failure with reduced EF (EF ≤ 40% (Systolic Heart failure)

→ mid-range EF: - LYEF 40-50%

Etiopathogenesis 00:18:41

- Etiology:

  Heart failure with reduced EF

  - Coronary artery disease
  - Regurgitant valvular lesions

- Obstructive valvular lesions
- Cor pulmonale
- Toxic → chronic alcoholism
- Prior viral infections
- Genetic causes of DCM

Heart failure with preserved EF

- Pathologic hypertrophy– Hypertrophic cardiomyopathies
  - Long standing HTN
- Restrictive cardiomyopathies – Infiltrative (amyloidosis)
  - Storage disorders (hemochromatosis)

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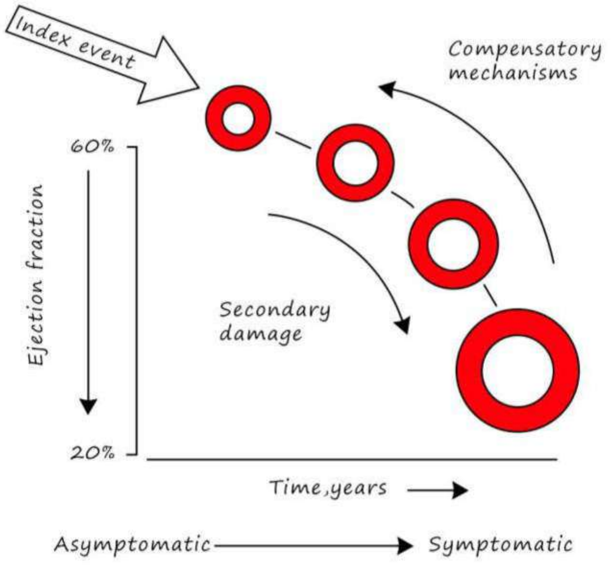
Pathophysiology

- Progressive reduction in EF
- Risk factor – acts as Index events — Acute - MI / Chronic - MR
- Myocardial dysfunction +

↓

Worsening of symptoms



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Why is there an asymptomatic phase?

- Because of compensatory mechanism → RAAS activation
  → vasodilatory substances
  ↓
  ANP, BNP, NO
  PGI_2 & PGE_2

LV Remodelling

- Occurs because of continued activation of — Neurohormonal / Adrenergic / Cytokine
- Results in adaptive changes in myocardium

Myocardial injury
↓
Loss of myocytes and increase myocardial strain
↓
Eccentric hypertrophy of remaining myocytes
↓
leads to – fibrosis
- Progressive LV dilatation
- Elliptical → spherical shape of LV
- Functional MR

Summary

- LV remodelling leads to increase myocardial oxygen consumption
  reduced efficiency of myocardial contraction
  Progression of HF

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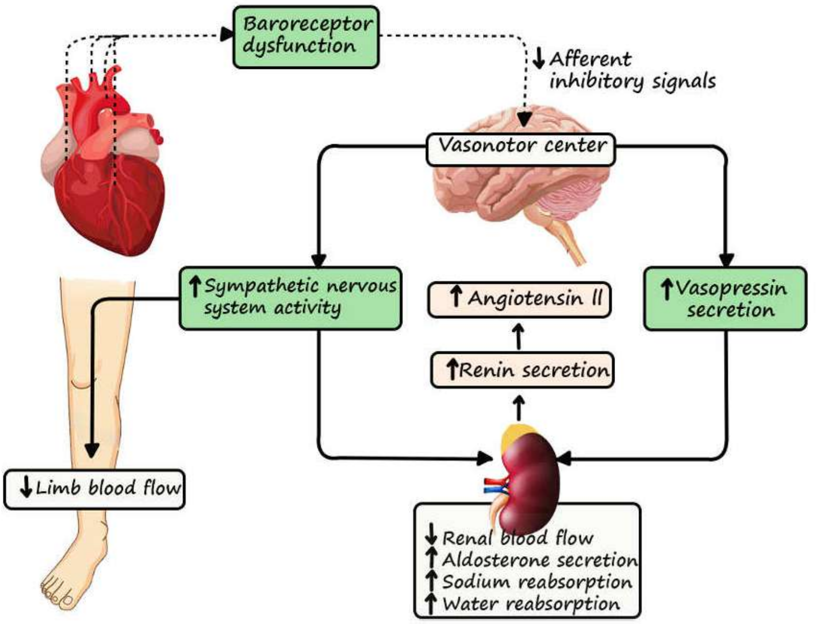

Heart failure with preserved EF

- Debatable
- Most important → creation of Proinflammatory state
- Occurs in patents with comorbidities → COPD, → CKD, → Type 2 DM] results in production of reacting oxygen species
  - → reduced NO bioavailability
  - → decreased protein kinase Activity

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SYMPTOMS & SIGNS

Symptoms 00:00:39

- Fatigue
- Breathlessness - orthopnea
  - PND (Paroxysmal Nocturnal Dyspnea)
- Palpitations
- Pedal edema
- Early satiety & abdominal bloating
- Anorexia
- Cognitive disturbances (sequelae of long-standing HF)
- Cardiac cachexia

Fatigue: - Low cardiac output
Skeletal muscle hypoperfusion

- Early stages – dyspnea an exertion
  Dyspnea @ rest (in later stages)

Why dyspnea?

- Accumulation of interstitial or intra-alveolar fluid

↓

Pulmonary congestion

↓

Activation of Juxtacapillary J receptors

↓

Rapid shallow breathing

Orthopnea: - dyspnea @ recumbent position

→ increase in venous return & lung congestion in supine position

→ increase pulmonary capillary pressure

→ Nocturnal cough

Proximal Nocturnal dyspnea (PND)

- Acute presentation
- When he goes to sleep, within 1-3 hours, he wakes up with acute onset of breathlessness & cough
- Mechanism: - orthopnea + depression of respiratory center in sleep

Cardia Asthma

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- Bronchospasm due to any cardiac cause
- Cheyne stokes respiration: - advanced cardiac failure

  ↓

  Other names: periodical /cyclic respiration

  Suggestive of poor prognosis
- Periods of Hyperventilation & hypocapnea

  ↓

  Apnea
- Changes in ARTERIAL PCO2
- In apneic phase → decrease arterial PO2, Increase arterial PCO2 → stimulates respiratory center

  ↓

  Hyperventilation & Hypocapnia

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Cachexia

- Due to – intestinal congestion
  - Chronic cytokines release & inflammatory mediators

Palpitation

- Reduced effort tolerance
- Tachyarrhythmias
- Right upper quadrants pain → liver congestion
- Cerebral hypoperfusions → confusion, disorientation
- Past history → cardiac disease – CAD / Valvular hear d/s / Congenital hear disease
  - → systemic illness → amyloidosis
    - → sarcoidosis
  - → Risk factors → Type 2 DM
    - → HTN
    - → obesity
- → H/O recent viral illness
  - → HIV/parasitic infection
  - → Non cardiac illness → Anemia / → Thyrotoxicosis / → Av fistula – High output states

Signs 00:22:25

- Sinus Tachycardia
- Systolic BP- Early Heart failure → Normal or high
  - Advanced HF→ reduced (LV dysfunction)
- Cold peripheral extremities
- Cyanosis

- Elevated JVP (increased RA pressure)
- Giant V waves in JVP – TR
- Displaced apex beat – LV dilation
- Pan systolic murmur – MR /TR
- 3rd heart sound → Gallop rhythm (Increase LA pressure)
- Lung crepitations → LA pressure & lung congestion
- Hepatomegaly → sequalae of increase RA pressure
- Hepatojugular reflex → increase RA pressure
- Pleural effusion (Transudative type)
- Ascites
- Peripheral edema

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TREATMENT OF HEART FAILURE

- Modified Framingham criteria
- Nhanes criteria

Modified Framingham clinical criteria for the diagnosis of heart failure

Major

- Paroxysmal nocturnal dyspnea
- Orthopnea
- Elevated jugular venous pressure
- Pulmonary rales
- 3° heart sound
- Cardiomegaly on chest radiograph
- Pulmonary edema on chest radiograph
- Weight loss >4.5 kg in 5 days in response to treatment of presumed heart failure

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Minor

- Bilateral leg edema
- Nocturnal cough
- Dyspnea on ordinary exertion
- Hepatomegaly
- Pleural effusion
- Tachycardia (heart rate >120 beats/min)
- Weight loss 24.5 kg in 5 days

- 2 majors

  (or)

- 1 major +2 minor

NHANES Criteria

Category	NHANES CRITERIA Criteria	Score
History	Dyspnea: When hurrying on a hill When walking at an ordinary pace? Do you stop for breath when walking at an ordinary pace? Do you stop for breath when after 100 yards on flat ground?	1 1 2 2
Physical examination	Heart rate: 91-110 beats/min >110 beats/min Jugular venous pressure (> 6 cm H_2O): Alone PLUS, hepatomegaly or edema Rales: Basilar crackles Crackles more than basilar crackles	1 2 1 2 1 2
Chest radiograph	Upper zone flow redistribution Interstitial pulmonary edema Interstitial edema plus pleural fluid Alveolar fluid plus pleural fluid	1 2 3 3

- Heart Failure → score ≥ 3

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Management of Heart failure

General measures 00:05:04

- Dietary sodium restriction (2-3g/day)

  ↓

- Moderate – severe (<2g/day)
- Fluid restrictions
  - Hyponatremia (<130mEq)
- Calorie supplementation in cardiac cachexia
- Treatment DM, HTN
- Quit smoking, alcoholism
- Management includes → chronic heart failure with reduced EF
  → chronic heart failure with presented EF
  → acute decompensated heart failure

Chronic Heart Failure Reduced EF 00:09:00

- ACC- AHA guidelines → 2021 update

Established therapies →

i. ARNIS → PARADIUM -HF trial

(Angiotensin receptor blocker neprilysin inhibitors)

↓

(sacubitril/valsartan)

Nephrilysm Inhibitor/ angiotensin1 receptor antagonism

Block breakdown of natriuretic peptides

ii. ACE Inhibitors

iii. ARB'S

iv. Beta blocker

v. Loop diuretic

vi. Aldosterone antagonist

↓

Spironolactone, eplerenone

vii. Hydralazine /Isosorbide dinitrate

viii. Ivabradine =→ If channer blocker

→ preferred agent → EF < 40%

↓

Indication: - NVHA class II-IV

Benefits of ARNI

→ Improves diastolic function

→ LV systolic function improvement

→ reduce incidence of ventricular arrhythmias

→ Quality of life improved

→ caution for ARNI → volume of depleted cases

↓

Postural HTN

→ Digoxin → rate control in AF

→ Heart failure with low BP

Wet	Dry
- ARNI /ALFI/ARB	- β blocker ↓ Carvedilol Metoprolol succinate Bisoprolol

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Ivabradine

→ EF < 35 %

→ on maximum to tolerated dose of β blockers

→ HR > 70/min

→ Target HR: - 50-60 /min

< 50% /min → discontinue Ivabradine

New drugs

- SGLT2 inhibitors → Dapagliflozin
  → empagliflozin
  } Hear Failure with or c/o T2DM NYHH II- IV
- Dapagliflozin: _ GFR > 30 ml/min
- Empagliflozin: - GFR > 20 ml/min
- Stage A→ treatment HTN
  DM, hyperlipidemia
  → ACE Inhibitors
- Stage B & C → goals → Reduces symptoms
  → prolong survival
  → Improve quality of life
  → prevent disease progression

NYHA 1

↓

Target neuro hormonal system

NYHA II-IV → neurohormonal system + diuretics

→ Initial therapy → Diuretics
→ ARNI/ACEI/ARB/
→ β Blockers
} combination

Loop diuretics

- Frusemide
- Torsemide (5-10 mg
- Bumetanide

act on Na^{+} K^{+} $2Cl^{-}$ symporter/co transporter

- Oral bio availability of frusemide- 50 %
- Diuretic s→ negative sodium and water balance

Cardiac Resynchronization therapy

- Mechanical synchrony abstained
- CRT/CRT-D
- Patient with NYHD class II-IV
  - EF < 30 % with wide QRS
  - Already on optimal medial therapy
- Stage D- mechanical circulatory support → VAD, IABP, ECMO
  - Continuous IV ionotropic support
  - Cardiac transplantation

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Hearth Failure with PEF 00:41:26

- No clear morbidity & mortality benefit
- control congestion by giving diuretics and other general treatment

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EVALUATION

Basic lab Investigations 00:00:41

- CBC
- Urine R/E
- S. electrolytes
- B, urea, S. creatinine
- Blood glucose level
- Fasting lipid profile
- LFT, TFT

ECG: - 00:03:58

- Ascertain cardiac t=rhythm
- LVH
- Prior MI

CXR 00:04:40

- Size and shape of heart
- State of pulmonary vasculature
- Non cardiac causes ruled out
- Pulmonary edema → Bat wing/Butterfly pattern
  → Kerly B lines

Natriuretic peptides 00:07:24

- BNP
- NT Pro BNP

→ Very sensitive marker for Heart Failure with EF
→ Excellent sensitivity and NPV
→ Prognosis and diagnostic uncertainty
→ Marker for optical dosing of medical therapy

- Soluble ST 2
- Galectin – 3

Causes of Elevated Natriuretic Peptide Levels

Cardiac	Noncardiac
• Heart failure, including RV syndromes • Acute coronary syndrome • Heart muscle disease, including LVH • Valvular heart disease • Pericardial disease • Atrial fibrillation • Myocarditis • Cardiac surgery • Cardioversion	• Advancing age • Anemia • Renal failure • Pulmonary causes: obstructive, sleep apnea, severe pneumonia, pulmonary hypertension • Critical illness • Bacterial sepsis • Severe burns • Toxic metabolic insults, including cancer chemotherapy and envenomation

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Other noninvasive diagnostic 00:14:04

- Echo
- MRI
- Cardiac CT
- Nuclear imaging

Echo: -

- assessment of – ventricular function
  - Size
  - Wall thickness
  - RWMA
  - Valve function
  - Decrease EF

MRI

- Better tissue characterization & spatial resolution
- Evaluates → cardiac morphology
  - Chamber sizes
  - Cardiac function
- Useful in inflammatory and infiltrative conditions
- Gold standard for assessment of LV mass & volume

Cardiac CT

- Determines obstructive CAD - By CT Angio
- Useful for CRT lead placement

Nuclear imaging

- SPECT & PET → assessing myocardial ischemia & viability

FDG PET

- Cardiac sarcoidosis
- Tc 99
- Useful for TTR amyloidosis

I123 MIBG Scan

- For evaluation of sympathetic function

Invasive Evaluation 00:23:22

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- Right heart catherization
  ↓
- Selecting patients of CT
- Patient with significant hypotension
- Patients with significant hypoperfusion
- Dependent on ionotropic infusions
- Persistent symptoms

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Role of endomyocardial biopsy

- Amyloidosis
- Myocarditis

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JVP

- Jugular venous pressure: - refers to the pressure of the venous column
- Jugular venous pulse: - pulsations of the venous column
- Provides a rough estimate of the central venous pressure
- Also provides an estimate of volume status

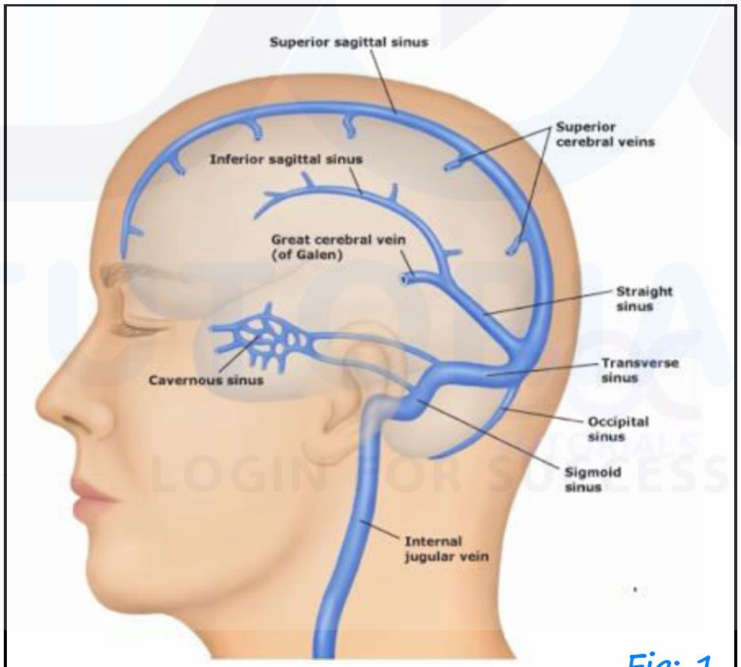

Fig: 1

- Internal jugular vein → direct continuation of the sigmoid sinus

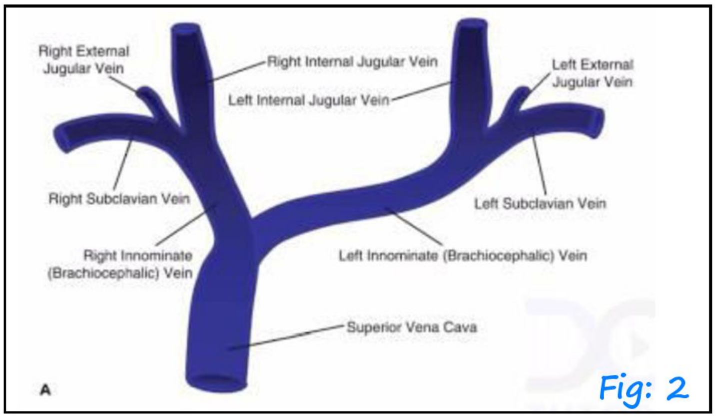

Fig: 2

- R and L Internal jugular vein join with subclavian vein and it results in the formation of R and L brachiocephalic vein (innominate vein)
- R and L Brachiocephalic veins join to form SVC
- Superior Vena cava into the Right atrium
- No valves in Brachiocephalic vein and Superior Vena cava
- When there is a R atrial contraction it causes pulsations in SVC, brachiocephalic vein and IJV
- Study of Pulsations of IJV will give an idea about the hemodynamics of the right side of the heart
- JV Pulsations Are Oscillating top of the distended IJV
- 2 important observations while studying JVP are
  - Study different waves of jugular venous pulsations
  - Study/measure jugular venous pressure
- Right IJV is used for the purpose

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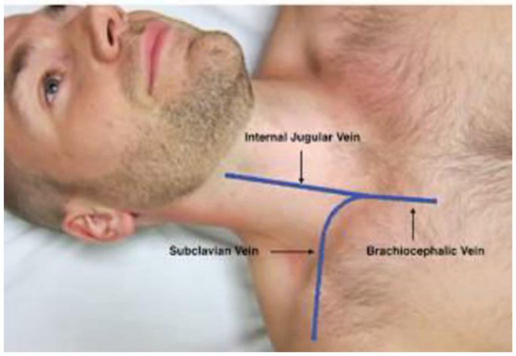

Fig: 3

- IJV lies lateral to the Carotid artery and deep to Sternocleidomastoid between sternal and clavicular head
- EJV cannot be used to measure JVP as it gets Compressed by structures in the neck and upper thorax and the presence of Valves. These factors interfere with the accurate transmission of pulsations
- R- IJV more in line in Right atrium
- Brachiocephalic vein more likely to be compressed by structures Like Aorta and sternum

Position of the patient:

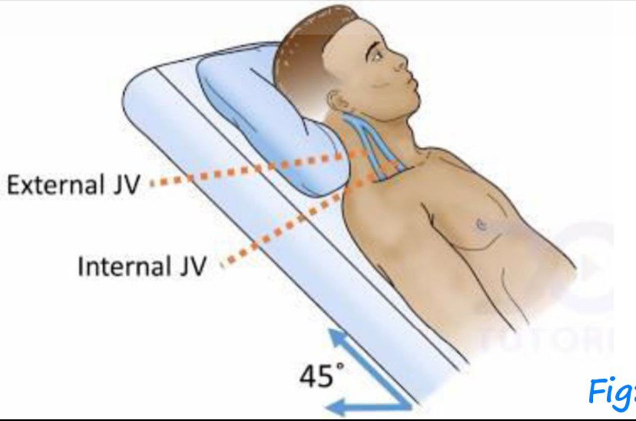

Fig: 4

- Patient should lie supine
- Elevation of upper part of the body by 30-45° from the bed
- Head and trunk are in the same line
- Normally JV Pulsations cannot be seen in sitting, standing positions as pulsations are occurring below the clavicle inside the thorax
- If Pulsations of IJV are seen in sitting or standing position-pressure is high
- JVP does not changes with change in position
- Position at which pulsations are best seen depends on pressure in the IJV
- Low Venous pressure: - position <15 °
- N. venous pressure: - 30-45°
- High volume pressure: - 60-90°

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Jugular Venous Pressure 00:17:04

- Vertical height in CMS of the oscillating venous column

Fig: 5

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- Anatomical landmark: - sternal angle (angle of Louis)
- sternal angle is at a constant distance of 5cm from centre of RA
- Sternal angle: - point where the costal cartilage of 2nd rib will articulate with sternum
- The distance between angle of Louis and R atrium can vary specially in obese persons

2 object method

Vertical object →always Scale | Horizontal object →scale

- Vertical distance from the sternal angle to lower border of horizontal object
- In normal individuals, the stop column is maximum 3 cm
- >9 cm H2O → Abnormal
- 1.36 cm H2O = 1mm Hg

Fig: 6

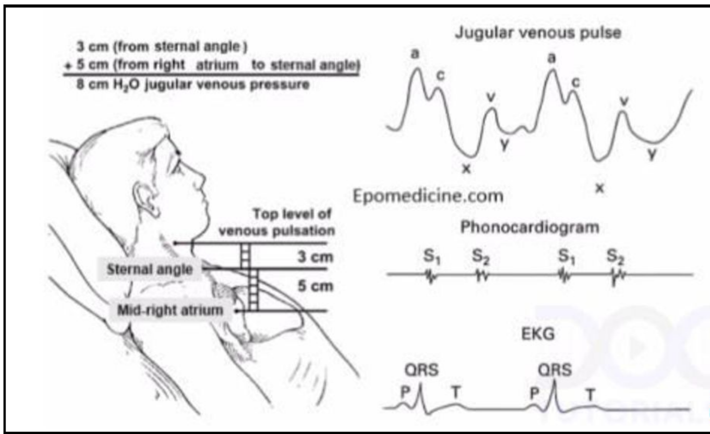

Fig: 7

Distinguishing jugular venous pulse from carotid pulse:

Feature	Internal jugular vein pulse	Carotid artery pulse
Appearance of pulse	• Superficial and more lateral • Undulating two troughs and two peaks for every cardiac cycle (Biphasic) • Descents are more prominent than crests	• Deeper and more medial • Single brisk upstroke (Monophasic)

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Response to inspiration	Height of column falls and troughs become more prominent	No respiratory change to contour
Palpability	Generally, not palpable (Except in severe TR)	Palpable
Effect of pressure	Can be obliterated with gentle pressure at base of vein/clavicle	Cannot be obliterated

Hepatojugular reflex:

- Abdominojugular reflex used to elicit venous hypertension
- Useful in Impending heart failure
- Pressure applied over R upper quadrant at least 10 seconds
- Rise > 3 cm in venous pressure which is sustained at least for 15 seconds -Positive Hepatojugular reflex
- Patient should not hold breath
- Gives indication if PAWP > 15 mm Hg

Kussmaul's sign

- N JVP fall by 3 mm Hg with inspiration
- Rise in venous pressure (or) a failure to decrease of JVP during inspiration is Kussmaul's sign
- Seen in
  - Constrictive pericarditis
  - Restrictive cardiomyopathy
  - Pulmonary embolism
  - RV infraction
- Seen in R sided volume overload& reduced RV compliance

Waves of JVP 00:35:05

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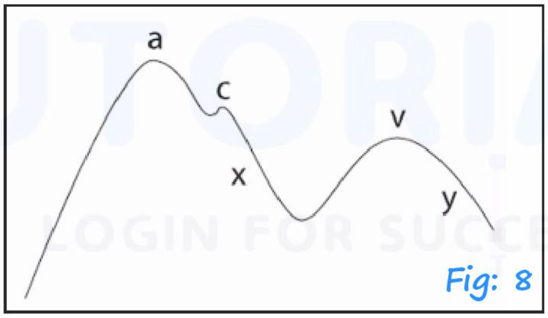

Fig: 8

- 3 positive waves
  - a wav → most prominent wave
  - c wave
  - v wave
- 2 Negative waves

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- x descent → most prominent wave
- y descent

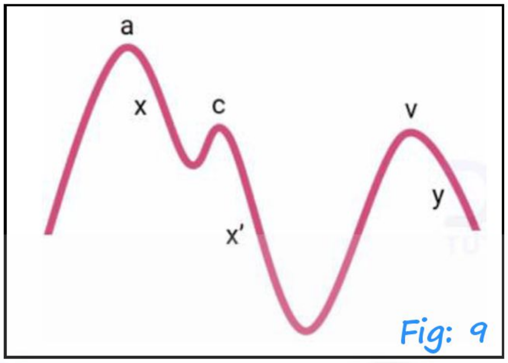


Fig: 9

- x'→X prime
- JVP waves in relation with cardiac cycle:

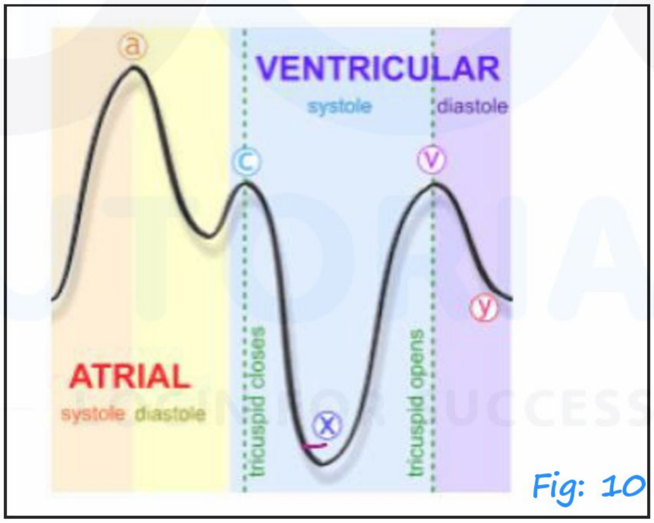
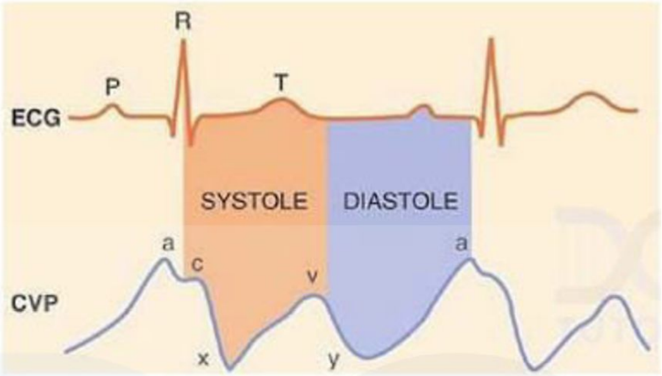


Fig: 10

- a wave: (a- atrial contraction) produced by R atrial contraction happens in atrial systole
- it happens in the Late phase of ventricular diastole (late filling phase)

- Comes before carotid pulse and first heart sound (presystolic wave)
- Comes after P wave of ECG



JVP IN RELATION WITH ECG Fig: 11

Abnormalities in a wave:

- Absent a wave is seen in atrial fibrillations
- Giant a wave occurs when R atrium contract with increased force Usually in diastole
  - RVH
    ↓
    Decreased compliance
    ↓
    Occurs 2° to pulmonary hypertension
  - TS
  - LVH (severe aortic stenosis)

Canon Wave

- Occurs when R atrium contracts with closed tricuspid valve

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  - Irregular cannon waves in complete heart block, VT
  - Regular cannon waves in Junctional rhythm
- Systolic in time

C Wave

- It is due to tricuspid valve bulging into RA isovolumetric contraction

X- Descent

- Due to Fall in RA pressure
- Due to atrial relaxation, downward movement of the tricuspid valve during RV systole
- Atrial diastole
- X- relax
- More prominent during inspiration
- Ends before S2
  - Absent X Descent →in Tricuspid regurgitation → Atria is not able to relax
  - Prominent x descent → in Cardiac tamponade
  - IN CARDIAC TAMPONADE:

    Fluid around the heart

    ↓

    Vigorous RV Contraction

    ↓

    Floor of the RA, Tricuspid valve pulled down

    ↓

Significant decrease in RA Pressure

V wave

- Begins in late systole and ends in early diastole
- Roughly corresponds to S2
- Because of venous return
- A wave – carotid – V wave

Abnormalities of v wave:

- Hypovolemia– absent V wave
- Hypervolemia – prominent V wave
- Giant V wave – Occurs in TR
  - during RV systole – These is regurgitation of blood from RV to RA leads to significant increase in RA pressure
  - In severe TR- Positive regurgitant wave fuses with v wave

↓

ventricularization of waveform

↓

giant v wav

  - D/d – Carotid pulsation
  - Lancisi's sign – refers to large systolic JVP Caused by TR replacing the normally occurring X descent
  - Also referred as C-V waves

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y Descent

- Tricuspid valve Opens

  ↓

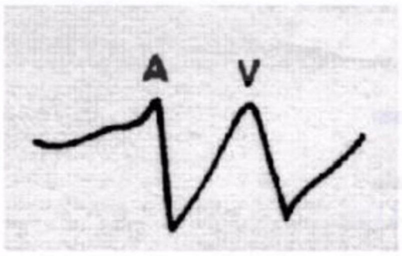
  rapid flow of blood from RA to RV in early diastolic filling phase

  ↓

  Fall in RA pressure – y Descent

Abnormalities of y descent:

- Prominent y descent:
  - Constrictive pericarditis –mid, late diastolic resistance and Normal early diastolic filling
  - TR
- Absent y descent
  - Cardiac tamponade
  - No diastolic filling
- Friedreich sign- sharp & step y descent seen in constrictive pericarditis



W sign Fig: 12

- Slow y descent:

- Tricuspid stenosis
- R atrial myxoma

H wave

- Brief positive wave
- Follows y descent
- Prior to a-wave
- Seen when diastole in too long
- SVC Obstruction
  - Raised non – pulsatile JVP

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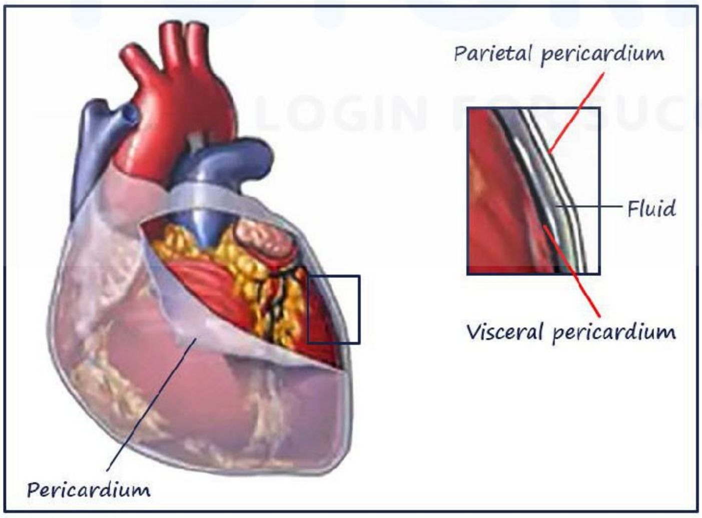
ACUTE PERICARDITIS

Introduction 00:00:27

- Normal pericardium is a double layered fibroelastic sac
- 2 layers – Inner visceral pericardium
  Outer parietal pericardium
  } In between these two → Pericardial space

- Pericardial space is filled with in 15-50ml of serons fluid is called as pericardial fluid is called as pericardial fluid of function (delete)
- **FUNCTIONS :**
- Acts as barrier to prevent infection to heart
- Pericardium exerts restraining force that sudden dilation chamber is prevented



15-50ml of serous fluid

Disease affecting pericardium

- Acute pericarditis
- Pericardial effusion **which can lead to cardiac** tamponade
- Constrictive pericarditis

Pericarditis 00:03:51

- Inflammation of pericardium
- Based on duration of clinical course

Acute	Subacute	Chronic
<6weeks	6W-6M	>6months

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Etiologies:

- Idiopathic
- Infections (Viral, Bacterial, TB, Fungal, Parasitic)
- Inflammatory conditions
  - Connective tissue disease (SLE)
  - Drugs like procainamide, hydralazine
- Renal failure (uremic pericarditis)
- Acute MI
- Post MI (Dressler's syndrome)
- Post radiation
- Neoplasm (Mets from Ca lung, Breast)

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Dressler's syndrome

- Also known as post myocardial infraction syndrome
- Occur usually 1-8 weeks after Myocardial infarction
- It is an auto immune response to antigens released by dead myocytes
- Clinical features: Fever, Pleuritic chest pain, Leucocytosis, elevated ESR.
- Treatment :
- Aspirin
- Steroids, NSAID's are avoided as they interfere with in healing process

Clinical features of Acute Pericarditis 00:10:04

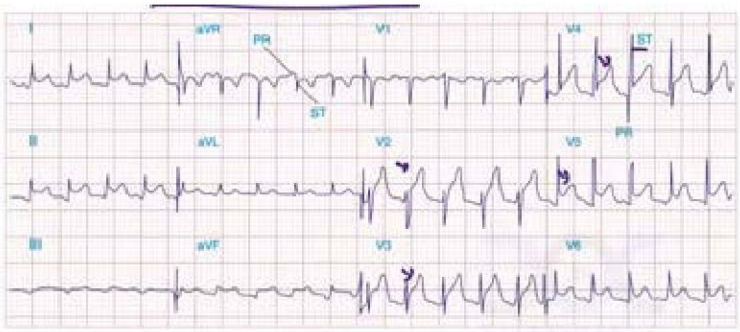
- Most common symptom is chest pain – Pleuritic type (Increases with in coughing)
- Retrosternal/Left precordial region.
- Trapezius ridge (Classic radiation site)
- Increased on lying supine
- Decrease on sitting up (or) leaning forward
- Pericarditis due to TB, Uremia, post irradiation, Neoplastic usually are painless.
- **Dyspnoea**
- Cough
- Hiccough

On examination:

- Pathognomic physical sign: Pericardial Rub
- It is due to friction between pericardial layers
- Loudest at lower left sternal boarder
- Best heard on patient learning forward and at end expiration
- Pericardial rub has 3 components
  - Ventricular Systole
  - Ventricular diastole
  - Atrial Systole
- Quality of the pericardial rub is scratching, grating, rasping.
- Pericardial rub is similar to sound made while walking on a crunching snow

Evaluation 00:17:46

- ECG :
  - Diffuse ST segment elevation except lead aVR, V1
  - ST segment vector → anteriorly leftward inferiorly



- It evolves through 4 stages:

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1.Wide spread ST segment elevation

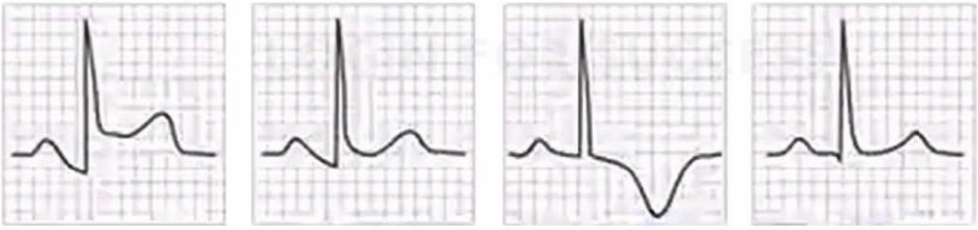
- Concave upwards
- Reciprocal depression in aVR, V1
- Depression of PR segment below the TP segment due to involvement of pericardium overlying the atria
- QRS complex normal
- DD: Acute STEMI

- STEMI : ECG Features:
  - ST ↑ in convex upwards
  - Prominent reciprocal depression
  - Q waves

2.ST segment return to normal.

3.T wave inversion

4.ECG is normal



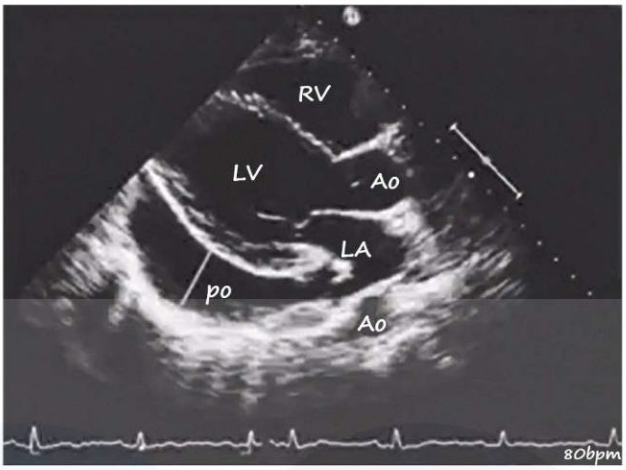
Stage I   Stage II   Stage III   Stage IV

Chest X-ray:

- In uncomplicated A/C pericarditis – CXR is normal
- Cardiomegaly in case of effusion

Echocardiography:

- To look for effusion



High sensitivity CRP:

- Elevated in inflammatory/**Infectious** causes

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MRI (or) CT:

- Useful in loculated effusion and pericardial thickening

Treatment 00:28:34

- Identify the cause & treat it
- In acute idiopathic pericarditis – No specific treatment
- Empiric anti inflammatory therapy
- Aspirin, Ibuprofen, Colchicine
- Steroids have limited role except in CTD, Renal failure (or) non responsive to anti-inflammatory therapy
- Avoid anticoagulants

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- In Refractory/Resistant causes
- Azathioprine
- Anakinra (IL-1 Receptor antagonist)

Complications:

- Effusion → Tamponade
- Constrictive pericarditis

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CARDIAC TAMPONADE

- Accumulation of pericardial fluid under pressure

↓

Impairment in cardiae filling

↓

Hemodynamic compromise

- It is a mechanical consequence of increased intra-pericardial pressure

Etiology 00:02:17

- Idiopathic pericarditis
- TB
- Neoplasm
- Post-cardiac surgery
- Trauma
- Patient on treatment with anticoagulants

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Pathophysiology 00:04:05

- Increased intra-pericardial pressure

↓

Diastolic compliance is decreased

↓

Significant limitation to ventricular filling

↓

Decrease in CO

- Rapidity of development of effusion is important
- In severe tamponade, equalization of pressures of right and left-sided heart chambers
  (Mean filling pressures: 20-25mm Hg)

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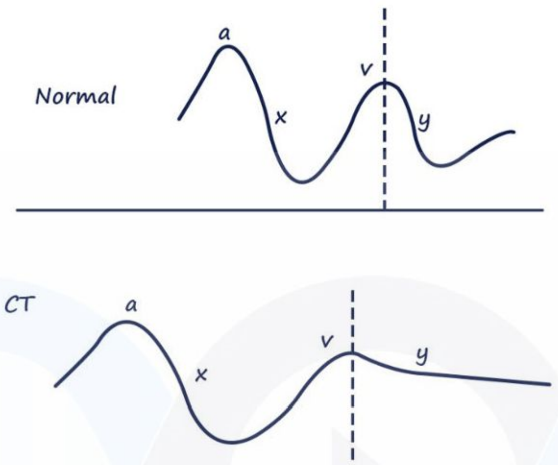
- **2 Characteristic hemodynamic abnormalities**
  - Absent y descent in JVP
  - Pulsus paradoxus / paradoxical pulse



In cardiac tamponade

- Fluid in pericardial space does not allow the ventricles to relax

  → **absent y descent**

- There is a fluid around the ventricle, Which causes pressure on ventricles

  ↓

  Vigorous contraction of right ventricle

  ↓

  Floor of RA pulled down

  ↓

  Prominent x descent

Pulsus paradoxus:

- Decrease in systolic BP>10mm Hg on inspiration
- Demonstrated with sphygmomanometer
- RV Volume increased on inspiration

↓

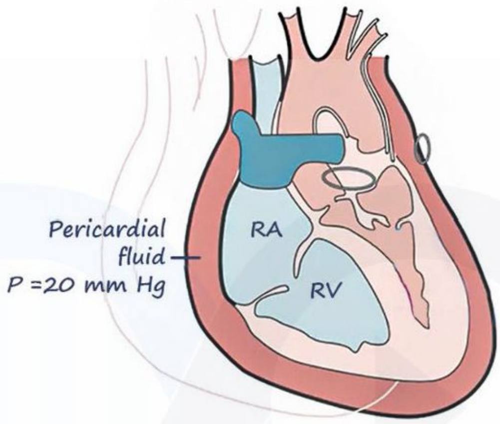
Pushes the IVS to left side

↓

LV is reduced

↓

↓ systolic BP



Seen in

1. 1/3rd of patients with CP
2. Hypovolemic shock
3. Obstructive airway disease like BA
4. Pulmonary embolism

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Clinical Features 00:18:02

- Dyspnea

Becks triad

1. Hypotension
2. Soft or absent heart sounds
3. Elevated JVP
   - Absent y descent
   - Prominent x descent

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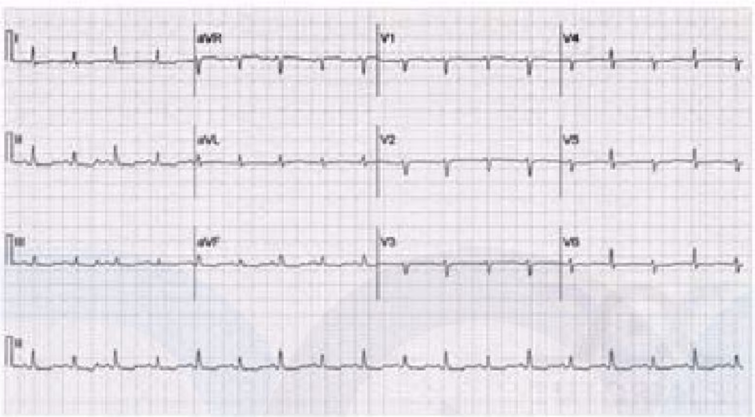
Investigations 00:19:28

ECG:

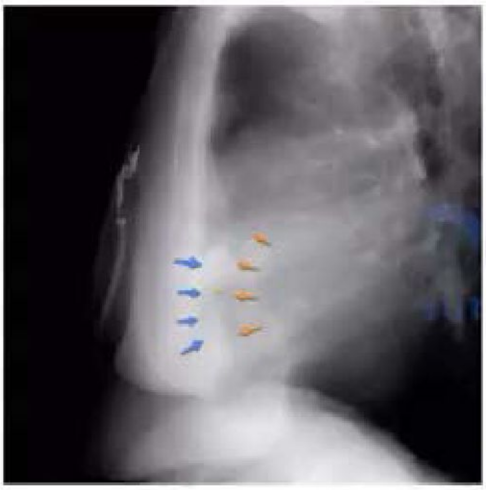
- Low voltage QRS
- **Electrical alternans** (beat to beat variation +) d/t Anteroposterior swinging of heart



Chest X-ray

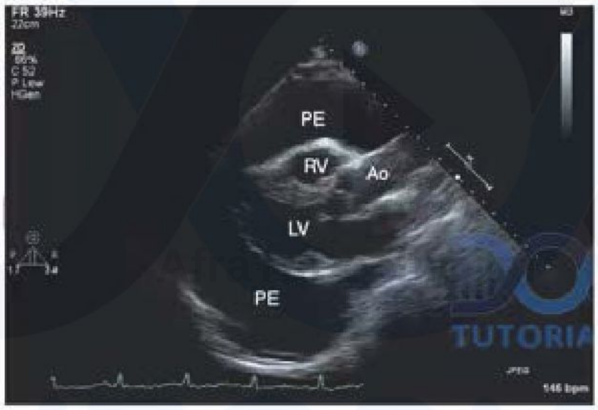
- Cardiac silhouette has rounded flask/ water bottle shaped appearance

- Pulmonary oligemia
- epicardial stripe>2mm- Oreo cookie sign / epicardial fat pad sign



ECHO:

- TTE: pericardial effusion +



- TEE, CT, MRI: useful in localised effusion

Treatment of CT 00:26:25

- It is a medical emergency
- TOC → **Closed pericardiocentesis** preferably done under echo guidance (until fluid is <25ml/day)
- Temporary measure:
  - IV Normal saline
  - Inotropes
- Analysis of pericardial fluid to establish etiology, check for TC, DC, Proteins, sugars

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- Bloody effusion seen in neoplasm TB
- Chylous effusion in rupture of thoracic duct
- Cholestrol rich effusion seen in hypothyroidism (gold paint effusion)

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CONSTRICTIVE PERICARDITIS

- It Is an end Result of Scarring & Loss of Elasticity of the Pericardial Sac

Etiologies:

- Idiopathic
- TB
- Post viral
- Post-cardiac surgery
- Post irradiation
- Neoplasia (Ca lung, Breast)
- SLE, RA
- All these etiologies lead to fibrous thickening of pericardium + calcifications

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↓

Pericardial non compliance

↓

Filling of all chambers of heart are affected

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Pathophysiology 00:03:31

Pericardial non compliance

↓

Increased diastolic pressures

Elevated equalised diastolic pressure in all chambers

↓

Marked restriction in filling of heart

(Normal filling in early diastole)

(Mid & late diastolic restriction)

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Note:

In cardiac tamponade:

- There is impaired filling throughout the diastole
- EDV, SV reduced
- ED pressure, MAP is elevated
- Systolic function is relatively normal
- In advanced cases myocardium is involved

↓

Myopericarditis

↓

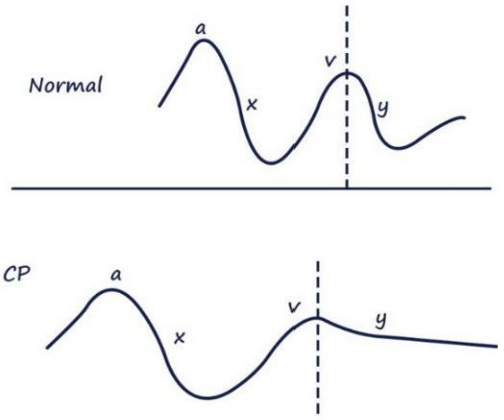
Symptoms& signs of venous congestion

Clinical features 00:08:29

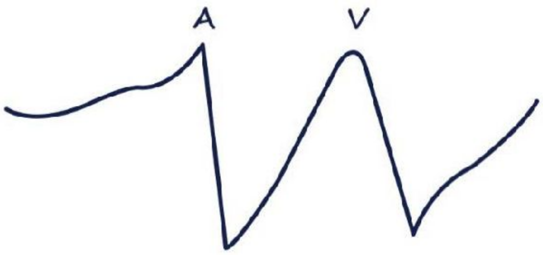
- Symptoms & signs of right heart failure
- exertional dyspnoea (dlt ↓ CO)
- Clinical course is usually chronic → Chronic Constrictive Pericarditis

Examination findings:

- Pulsus paradoxus is seen only in 1/3rd cases
- Elevated JVP: - Prominent, rapidly collapsing y descent



- **Friederichs sign:** sharp deep y- descent seen in constrictive pericarditis



W sign / M sign

- **Kussmaul's sign**
  - Normally JVP Should fall by 3mm hg with inspiration
  - Raise in venous pressure/ failure to reduce JVP is known as Kussmaul's sign
  - Broad bent's sign apical impulse retracts during systole

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- **Pericardial knock:**
  - It is early diastolic sound
  - Best heard in left sternal border cardiac apex
  - Occur earlier than S3
  - High frequency sound
  - Corresponds to early abrupt cessation of ventricular filling
- Congestive hepatomegaly
- Ascites
- Jaundice

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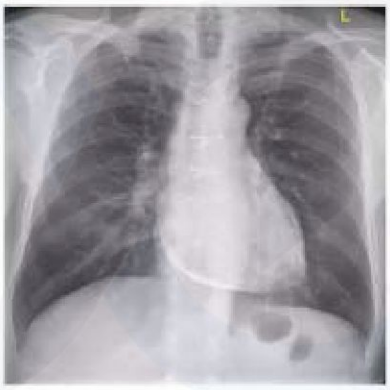
Investigations 00:16:28

ECG:

- Nonspecific changes
- Low volume QRS Complexes
- AF is seen in 1/3rd of patients

Chest X ray

- Normal / mild cardiomegaly
- Pericardial calcification in TB Pericarditis

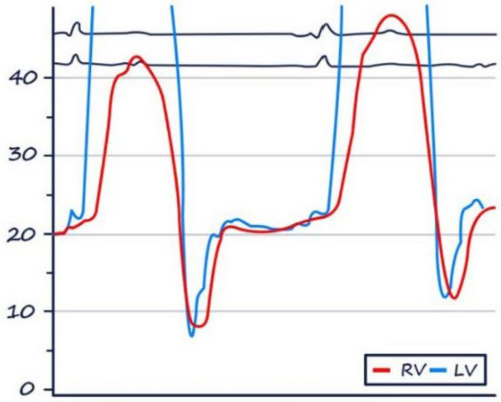


ECHO:

- Shows pericardial thickening
- Dilation of IVC, Hepatic veins
- Halt to LV Filling in early diastole
- Normal ventricular systolic function

Cardiac catheterisation:

- RV, LV Pressures show early marked diastolic dip followed by plateau → **Dip& plateau sign/square root sign**



Treatment of CP:

- Definitive Treatment- Pericardiectomy
- Temporary relief – Diuretics

Cardiac Tamponade vs constrictive pericarditis 00:22:01

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Characteristics	**Cardiac Tamponade**	**Constrictive pericarditis**
Clinical		
Pulsus paradoxus	+++	+
Jugular veins		
– Prominent Y descent	–	++
– Prominent X descent	+++	++
– Kussmaul's sign	–	+++
Third heart sound	–	–
Pericardia knock	–	++
Electrocardiogram		
Low ECG voltage	++	++
Electrical alternans	++	–
Echocardiogram		
Thickened pericardium	–	+++
Pericardial effusion	+++	–

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RV size	Usually small	Usually normal
Exaggerated respiratory variation in flow velocity	+++	+++

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AORTIC STENOSIS

- Aortic stenosis is the most common valve lesion in adults with chronic valvular HD

Types:

- Valvular As
- Sub-valvular As
- Supra valvular As

Etiologies 00:02:10

- Congenital bicuspid aortic valve
- Degenerative calcified aortic valve disease
- Rheumatic fever

} Active biologic process → Similar to vascular atherosclerosis

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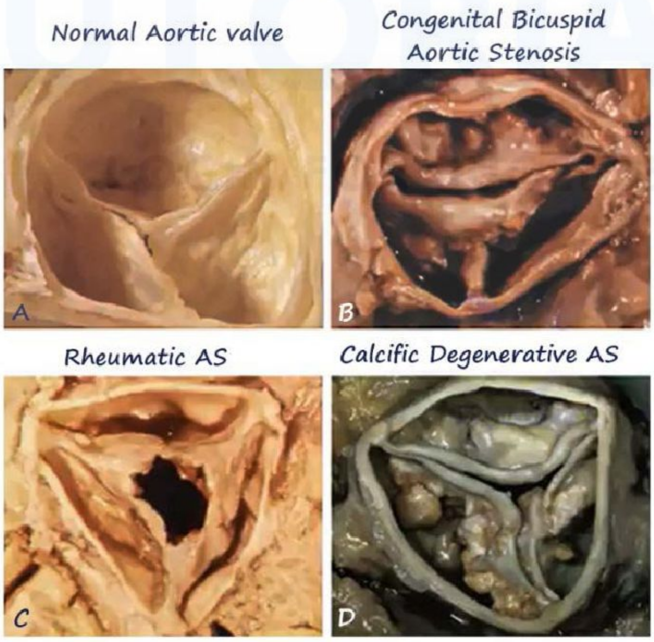

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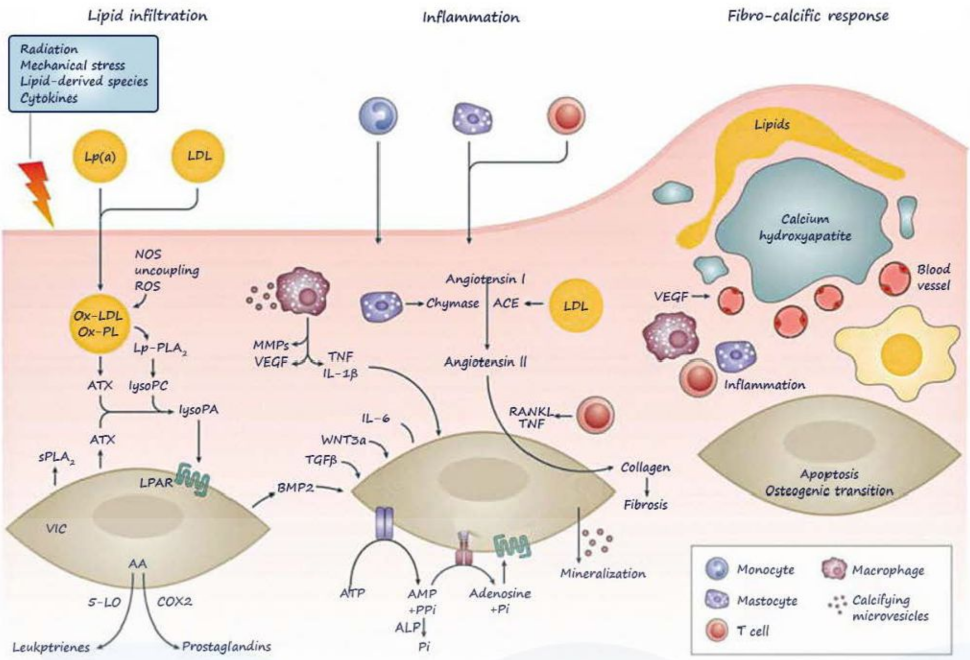

- Valve interstitial cells/ Valvular myofibroblasts in aortic valve

↓

Transforms into osteoblasts

↓

Formation of bone matrix protein

↓

Deposition of calcium hydroxyapatite in the form of nodules

↓

Calcification

- Rheumatic fever associated with coexisting mitral valve disease along with in AR

Congenital Bicuspid aortic valve:

- It is most common congenital heart valve defect
- AD, common in males

- Turner syndrome increases the risk
- It associated with AS, Aneurysm, Dissection

Pathophysiology: 00:11:18

- It is left ventricular outflow tract obstruction

↓

Creates a Systolic pressure gradient between LV& aorta (Trans-aortic valve pressure gradient)

↓

It decreases Cardiac output

↓

Adoptive response → Concentric LV hypertrophy (Maladaptive response) → Ischemia

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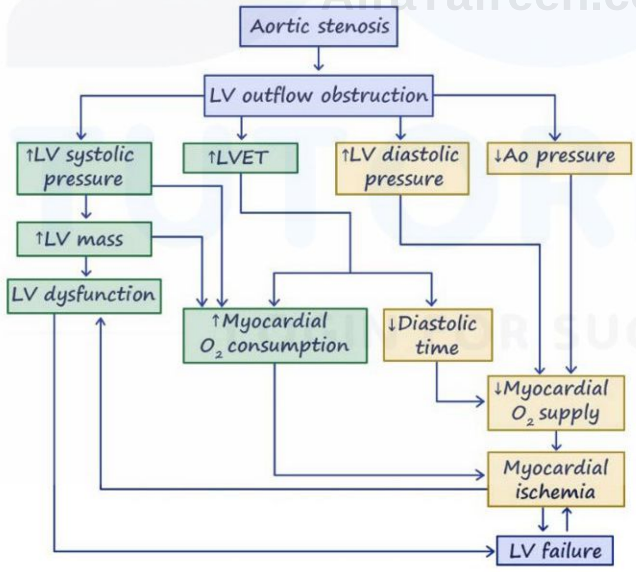

- Normal aortic valve orifice area: 3-4cm²
- Aortic stenosis <2cm²
- **Severe aortic stenosis** – Orifice area ≤ 1cm²

  – TAV pressure gradient >40mm Hg

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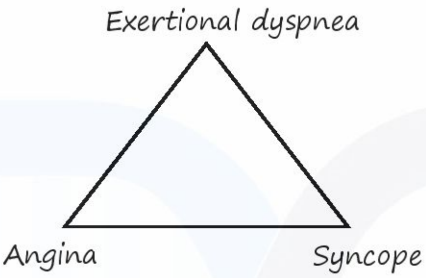
Clinical presentation 00:16:40

- Long asymptomatic period d/t compensatory Concentric LV hypertrophy
- Common age: **6th to 8th decade**
- Classical triad of AS

Classical triad of AS:



Dyspnea:

- Initially fatigue, decreased exercise tolerance, finally leads exertional dyspnea
- Dyspnea d/t LV diastolic dysfunction (↑ EDP leads to pulmonary congestion) and inability to ↑CO with exercise
- AS associated MS → Atrial fibrillation → Acute decompensation

Angina:

- d/t demand-supply mismatch
- Mimics angina of CAD (Precipitated by excursion relived by rest)
- Coexistent CAD may present

Syncope:

- d/t ↓CO → Cerebral hypoperfusion
- Sometimes presyncopal episode like mild dizziness giddiness, blackouts may present

Heart failure:

- Features of heart failure (LV or RV) seen in advanced severe AS

LV failure	RV failure
- Orthopnea - PND - Pulmonary oedema	- Pulmonary congestion

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Co existent AS + MS:

- MS lowers the TAV pressure gradient
- This can mask the findings of AS

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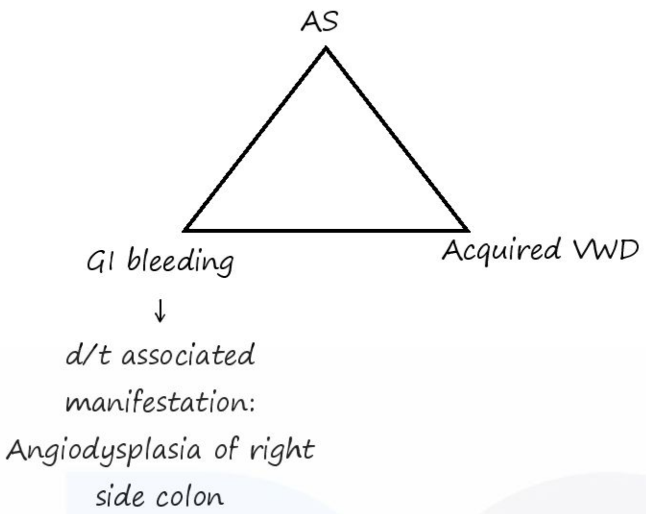
GI bleeding:

- Associated with **HAYDE syndrome**



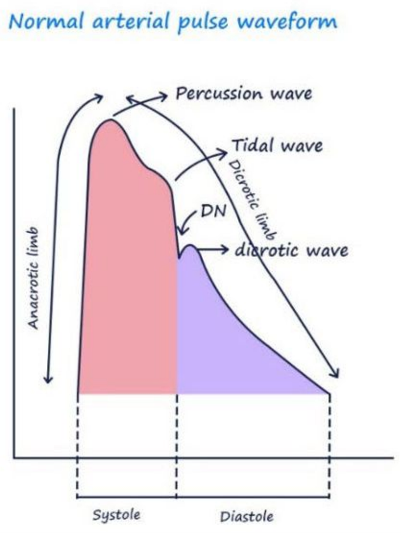
Infective endocarditis:

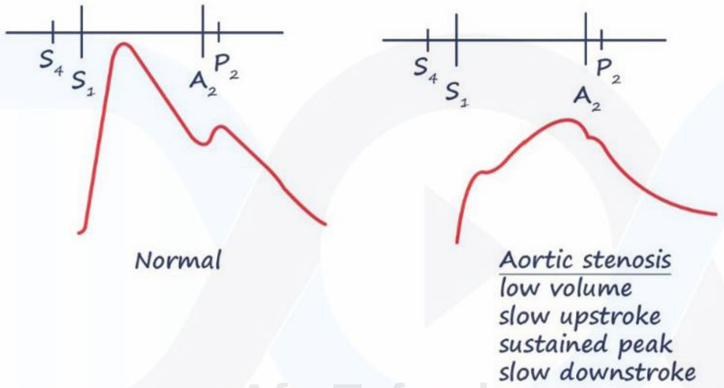
- Increased risk of IE in young pt with bicuspid aortic valve
- Small micro thrombi in BAV → Cerebral embolism & stroke

Examination findings 00:26:50

Pulse:

- Early stages – Normal
- Advanced cases → Low volume pulse
- Usually regular
- In case AF → Irregular pulse
- Character – **Slow rising late peaking pulse (or) "Pulsus parvus at tardus (or) Anacrotic pulse**





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- Appreciated by simultaneous palpation of carotid artery and apex, AS shows delay
- Thrill/carotid shudder: Palpable over carotid artery

Blood pressure:

- Lowering of systolic BP (or) systolic decapitation
- Narrow pulse pressure
- Systemic hypertension

JVP:

- A wave is prominent d/t LV hypertrophy

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Palpation of precordium:

Apex beat:

- Initially normal in location
- As disease progresses, it displaced laterally d/t LV concentric hypertrophy

Concentric hypertrophy	Eccentric hypertrophy
Apex displaces downwards	Apex beat displaced down & out

- Hearing apex (Reflection of pressure overload)

Systolic thrill:

- Mainly at base of heart towards the right of sternum and also at suprasternal notch
- Best felt in full expiration & pt leaning forward

Auscultation:

- S1 – Normal
- S2 – Abnormal
- In severe as → Prolongation of LV systole

↓

A2 occurs late, sometimes even after P2

↓

Paradoxical split of S2 or Single S2

Single S2 d/t:

- A2 coinciding with P2
- A2 is inaudible
  - S3: may present in LV failure
  - S4: Present d/t vigorous LA contraction against stiff Noncompliant ventricle

Ejection sound 00:42:19

- These are high frequency, clicky systolic sound
- Occurs d/t vibrations associated with opening of aortic and pulmonary valve
- It can be aortic or pulmonary ejection sound

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Aortic ejection sound:

- It is high frequency, clicking systolic sound and corresponds to upstroke of carotid
- Etiology
  - Congenital bicuspid aortic valve
  - Ascending aorta aneurysm
- Properties
  - It is widely transmitted
  - Best heard over apex
  - Can be heard over the base (2nd right ICS close to sternum)
- Intensity dose not vary with in respiration

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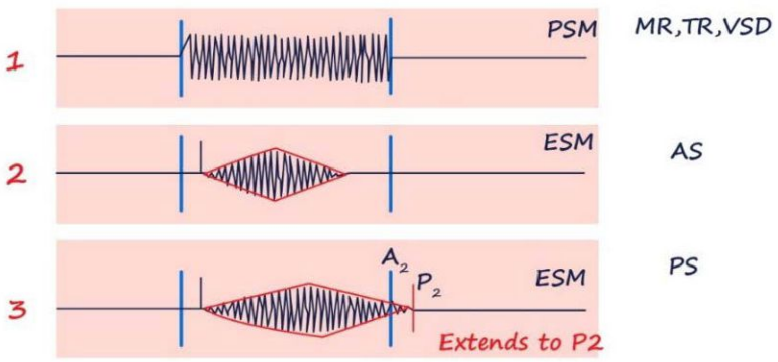
Pulmonary ejection sound:

- Etiology
  - PS
  - Idiopathic dilation of pulmonary artery
  - Chronic PAH
- Not widely transmitted
- Best heard at Lt 2nd ICS
- Intensity decreases with inspiration (This is only right sided cardiac event which decrease in intensity with inspiration)
- Note: **In calcified rigid aortic valve, aortic ejection sound is absent**

Murmur of AS 00:49:09

- **Ejection systolic/ Mid systolic murmur**
- Starts shortly after S1
- Increases in intensity, reaches peak at middle of ejection
- Subsequently it decreases in intensity and ends before aortic valve closure
- That's why it is called **Crescendo – decrescendo murmur (or) Dimond shaped murmur**



Differential diagnosis for ESM:

- AS
- PS
- HOCM
- Large ASD

Character of murmur:

- Low pitched, rough rasping type
- Loudest at the base of the heart (2nd Rt ICS)
- Radiates to carotids
- **Gallarvardin phenomenon**
  - As murmur radiates to apex
  - It has musical quality
  - It is DD of pansystolic murmur of MR

Correlation between murmur and severity of AS:

- Intensity

  Severe AS – Grade 3 or more
- Timing
  - Severe AS – late peaking murmur
  - mild to moderate as – early peaking murmur

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- Dynamic auscultation
  - In squatting → ↑stroke volume → Augmentation of murmur
  - In standing (or) strain phase of Valsalva → Attenuation or decrease in intensity of the murmur

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INTRODUCTION TO ANTERIOR PITUITARY GLAND

- *Master gland of endocrine orchestra*
- *Hypothalamus and pituitary orchestrate the entire endocrine system*

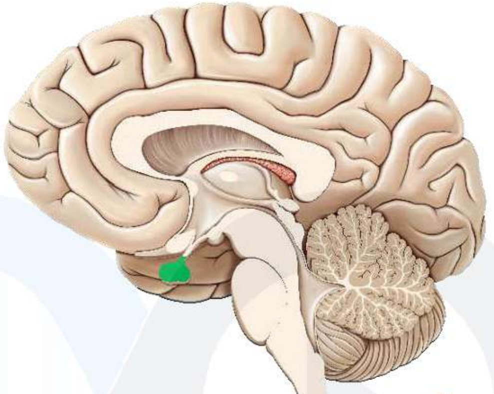

Fig: 1

- *Pituitary gland is located in Sella turcica near sphenoid bone*

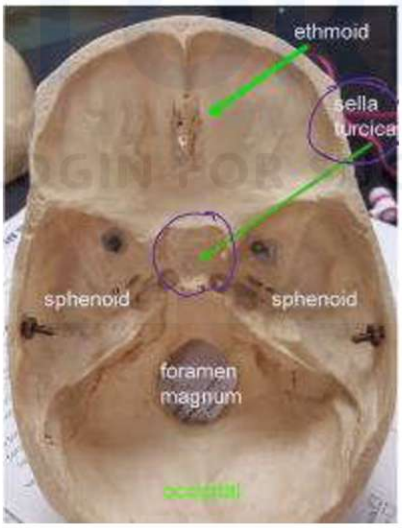

Fig: 2

- *Term Sella turcica is derived from Turkish saddle*

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Fig: 3

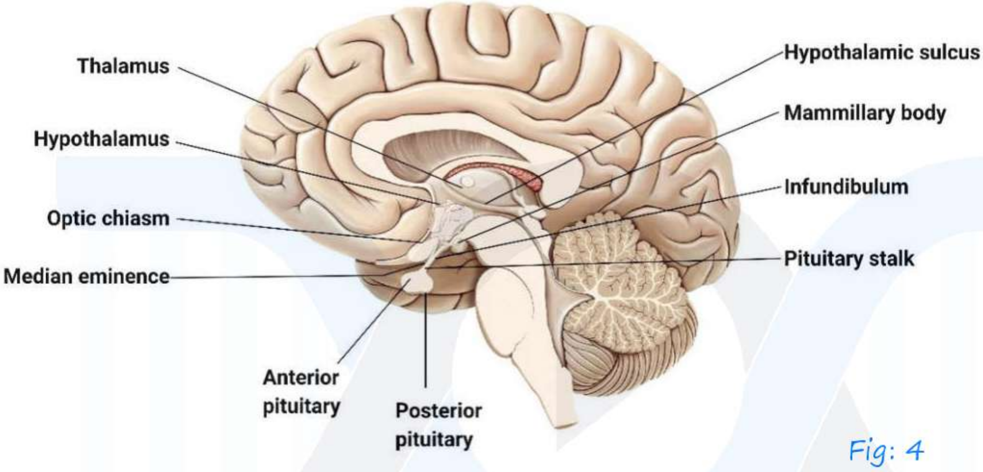

Fig: 4

- Pituitary gland
  - Anterior
  - Posterior
- Pituitary-stalk connects pituitary to hypothalamus

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Fig: 5

In T1 sequence

- Grey matter – Grey
- White matter – White
- CSF matter – Dark
- Posterior pituitary has hyperintensity normally in T1 sequence → Pituitary bright spot

Anterior pituitary 00:05:30

- Also known as adenohypophysis
- Cell types
  - Somatotrophs – GH (Most abundant)
  - Lactotrophs – Prolactin
  - Gonadotrophs – FSH, LH
  - Thyrotropes – TSH (Least abundant)
  - Corticotropes – POMC (Pro-opio melanocortin) → ACTH, MSH
- Q. First cell type to be formed – Corticotropes (6weeks of gestation)
- Q. GH is affected first
- All these hormones are under the control of hypothalamus

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Hormone	Under control of
GH	GHRH
Prolactin	Prolactin inhibiting factor (Dopamine) antipsychotics ↓ Inhibiting dopamine → Hyperprolactinemia
ACTH	Corticotropic releasing hormone
FSH-LH	Gonadotropin releasing hormone
TSH	Thyrotrope releasing hormone

Axis

- Hypothalamus

  ↓
- Pituitary

  ↓
- Effector organ

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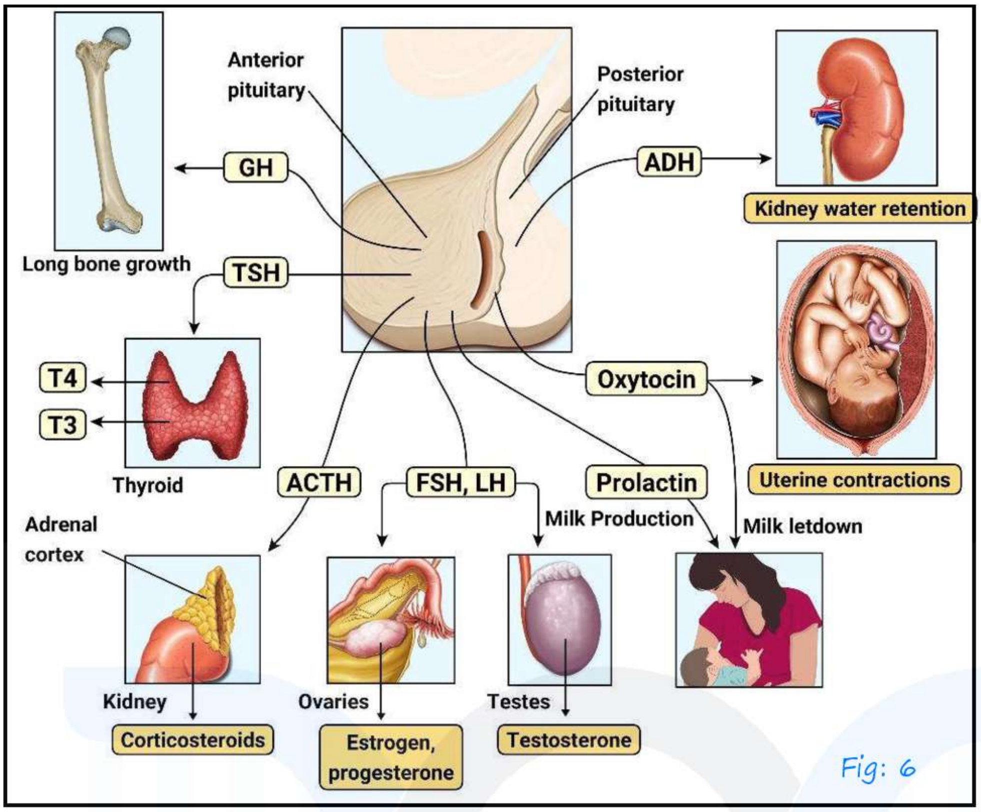

Fig: 6

Development 00:12:43

- Anterior pituitary – Adenohypophysis
- Posterior pituitary – Neurohypophysis
- Anterior pituitary → Remanent of Rathke's pouch
- Posterior pituitary → Extension from floor of 3rd ventricle

Blood supply

- 2 sources
  - Superior hypophyseal artery
  - Inferior hypophyseal artery

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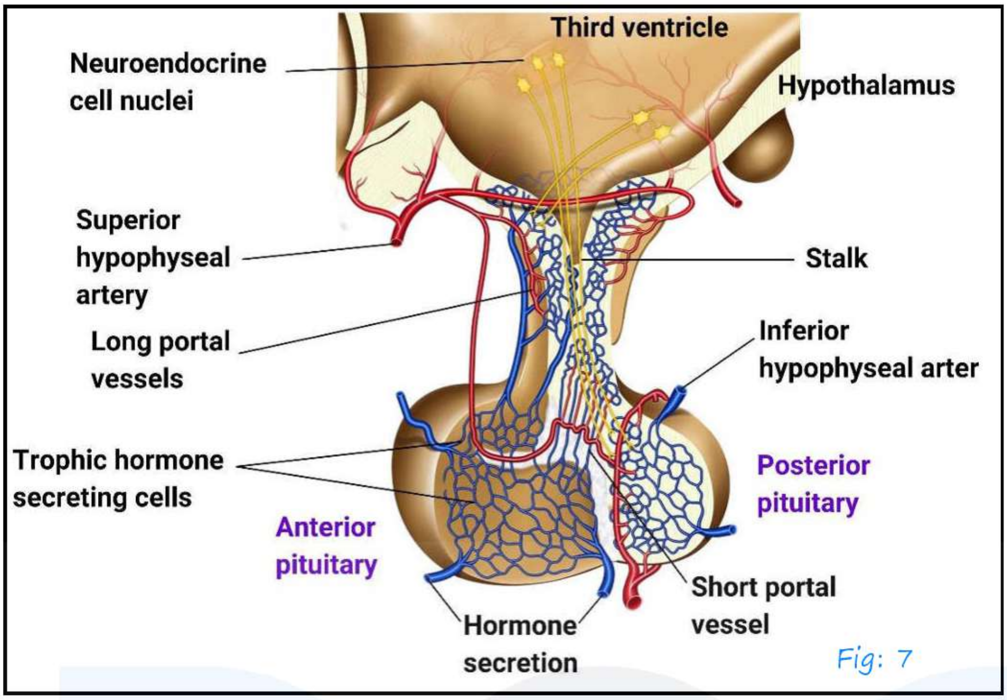

Fig: 7

- Superior hypophyseal artery a part of hypothalamohypophyseal portal system
- ADH – Antidiuretic hormone } Secreted by supraoptic nucleus
- AVP – Arginine vasopressin }
- Both these hormones reach the post pituitary via nerve fiber tract from hypothalamus
- These hormones are stored in post pituitary.

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CONGENITAL HYPOPITUITARISM

Hypopituitarism 00:00:05

- Basically, means decreased hormone secretion from pituitary.
- Can be either
  - Congenital
  - Acquired

Congenital causes of hypopituitarism 00:01:05

i. Pituitary dysplasia

- hyperplasia
- aplasia
- ectopic

→ midline skeletal abnormalities, cleft lip, cleft palate

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ii. Transcription factor defect

- For maintenance of cell lineages of anterior pituitary, transcription factors are needed.

↓

1. Pit-1
2. Prop-1

} defect → congenital hypopituitarism

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iii. Primary empty sella syndrome

iv. Hypothalamic syndromes

- Kallman syndrome – x linked KAL gene

Decreases GnRH → Decreases FSH, Decreases LH

Decreases Testosterone, estrogen

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Anosmia/Hyposmia

↓

Due to agenesis/dysgenesis of olfactory bulb

Renal anomalies

Cleft palate

- Bardet – Biedl syndrome
- Prader– willi syndrome

↓

Obesity, hypotonia, mental retardation diabetes mellitus

- Septo optic dysplasia
  → Dysplasia septum pellucidum
  → Optic nerve hypoplasia.

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ACQUIRED HYPOPITUTARISM

Etiology 00:00:19

i. Neoplasm

- Rathke's pouch
- Craniopharyngioma
- Pituitary metastasis

(Rathke's pouch, Craniopharyngioma — Mass lesions)

ii. Infiltrative Conditions

- Sarcoidosis
- Hemochromatosis
- Histiocytosis
- Amyloidosis

iii. Infective causes

- Histoplasmosis
- Toxoplasmosis
- Tuberculosis

iv. Cranial Irradiation

- First Hormone to be affective → GH > FSH, LH > ACYH > TSH

v. Lymphocytic Hypophysis's

D/D: - Pituitary macroadenoma

- Seen in postpartum
- Lymphocytic infiltration of pituitary → increases Pituitary size → May mimic Pituitary Adenoma → Headache Visual Disturbances

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- Treatment: - Good response to high dose glucocorticoids
- Is thought to be IgG4 disease

vi. Pituitary apoplexy

↓

Bleeding into pituitary

- Spontaneous bleed in an enlarged pituitary gland
- Post-partum (Sheehan's syndrome)
- Systemic HTN
- Sickle cell Anemia

Fig: 1

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Clinical Feature

- Headache
- Visual disturbances – Bitemporal hemianopia
  cardiovascular instability
- Hypotension / Shock

Treatment: -

- High dose glucocorticoids (Headache + Raised ICT)
  Surgical Decompression (Visual disturbances / Shock)

vii. Secondary Empty sella

- In pituitary tumor, there may be silent infarcts & Sub sequently pituitary tumor may undergo shrinkage

  ↓

  Region of sella may be occupied by CSF

  ↓

  Secondary empty sella syndrome

- Some years after Russets viper snake bite

  ↓

  Pituitary necrosis

  ↓

  Hypopituitarism

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Clinical Features

- Hormones affected → GH > FSH, LH > ACTH (According to Harrisons)

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GH Deficiency

- Children – dwarfism

  ↓

  GH deficiency

  GH receptor deficiency – Laron dwarfism

  GHRH receptor deficiency

- Adults – Nonspecific manifestations

  ↓

  Generalized slowners

  Fatigue

  Drive decreases

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Lipid profile changes

Increased risk of cardiovascular events

ACTH deficiency

- 2° adrenal insufficiencies
- Decreases cortisol – fatigue, Hypoglycemia
- Mineralocorticoid functions normal

FSH/LH

- Females: - Menstrual irregularities infertility
- Males: - Decreases Libido

  Loss of 2° sexual characteristics

TSH

- Children – Growth retardation short stature
- Adults – Classification features of hypopituitarism

Pituitary Function test

- TSH
- FSH / CH
- Prolactin

} Serum measurement

- GH
- ACTH

} Provocative test

GH – Provocative test

- Insulin tolerance test
- L. arginine ,L dopa

- GHRH

ACTH – provocative tests

- Insulin tolerance test
- CRH Stimulation test
- Metyrapone
- Cosyntropin test.

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PITUITARY TUMOURS

Introduction 00:00:05

- Mass effect
- Stalk section

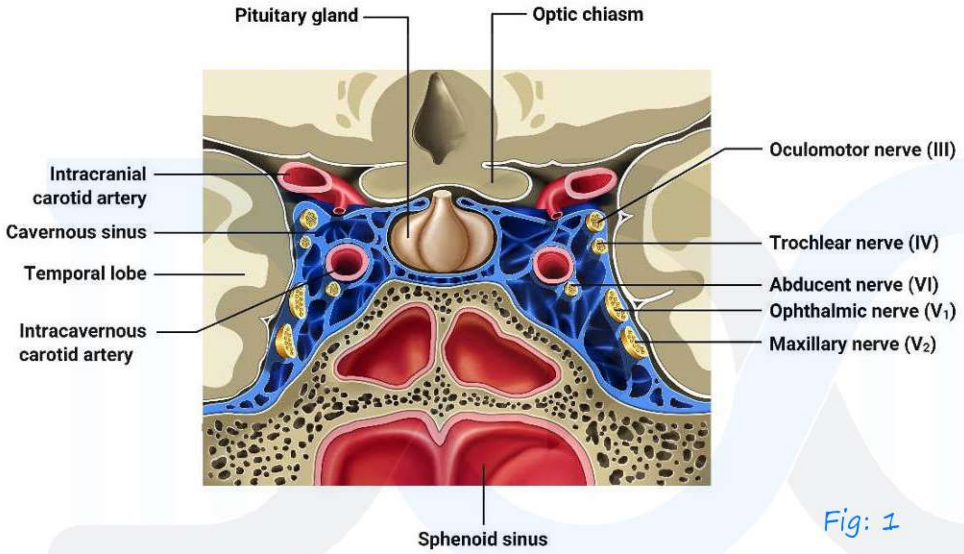

Fig: 1

- 10mm above pituitary gland – optic chiasma
- Pituitary enlarges predominantly superiorly and anteriorly

↓

Compress optic chiasma

↓

Bitemporal hemianopia

(Commonest visual field defect associated with pituitary adenoma)

- Pituitary enlarges anteriorly → optic nerve involved

- Pituitary enlarges posteriorly → retro chiasmal involvement (homonymous hemianopia)
- If it extends laterally → Involvement of cranial nerves in cavernous sinus (3rd, 4th, 6th)
  - Ptosis
  - Diplopia
  - Extraocular muscle palsy
- Rarely extends into sphenoid sinus

Features of sellar mass lesions 00:06:45

Impacted structure	Clinical impact
Pituitary	Hypogonadism Hypothyroidism Growth failure and adult hyposomatotropism Hypoadrenalism
Optic chiasm	Loss of red perception Bitemporal hemianopia Superior or bitemporal field defect Scotoma Blindness
Hypothalamus	Temperature dysregulation Appetite and thirst disorders Obesity

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	Diabetes insipidus Sleep disorders Behavioural dysfunction Autonomic dysfunction
Cavernous sinus	Ophthalmoplegia with or without ptosis or diplopia Facial numbness
Frontal lobe	Personality disorder Anosmia
Brain	Headache Hydrocephalus Psychosis Dementia Laughing seizures

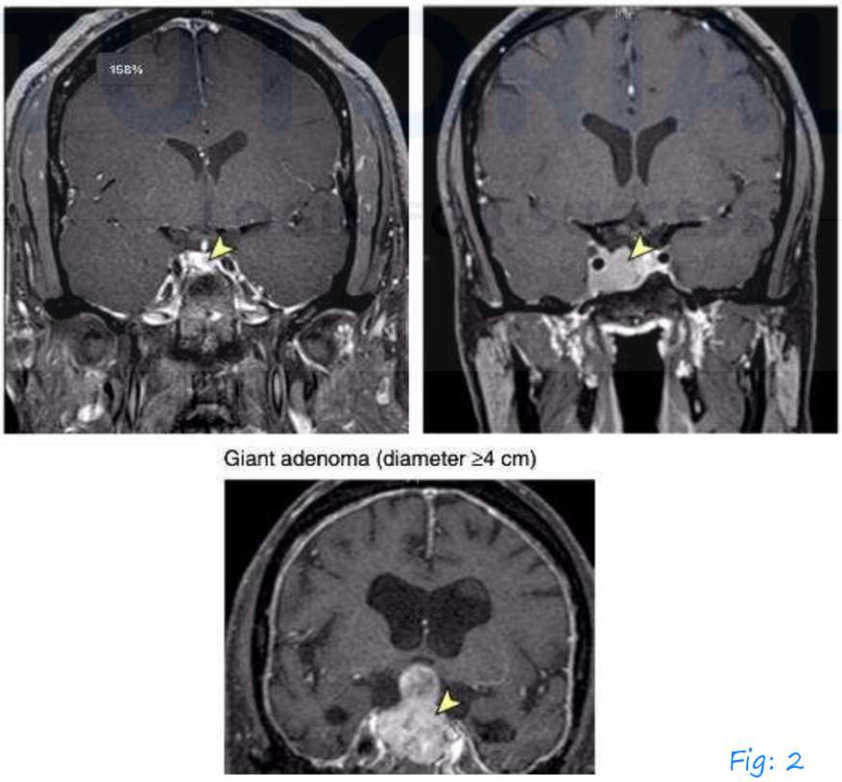

Fig: 2

- Tumors of pituitary can be
- Microadenoma (diameter <1cm)
- Macroadenoma (diameter ≥1cm to <4cm)
- Giant adenoma (diameter ≥4cm)

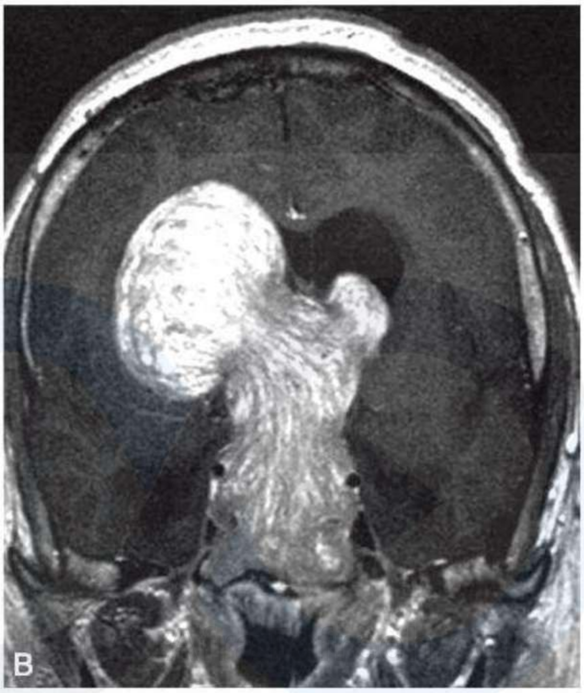

Fig: 3

Pituitary tumors 00:09:26

Adenoma cell origin	Hormone product	Clinical syndrome
Lactotrope	PRL	Hypogonadism, galactorrhea
Gonadotrope	FSH, LH, subunits	Silent or hypogonadism
Somatotrope	GH	Acromegaly/gigantism

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Corticotrope	ACTH/none	Cushing's disease or silent
Mixed growth hormone and prolactin cell	GH, PRL	Acromegaly, hypogonadism, galactorrhea
Other plurinominal cell	Any	Mixed
Acidophil stem cell	PRL, GH	Hypogonadism, galactorrhea, acromegaly
Mammosomatotrope	PRL, GH	Hypogonadism, galactorrhea, acromegaly
Thyrotrope	TSH	Thyrotoxicosis
Null cell	None	Pituitary failure/none
Oncocytoma	None	Pituitary failure/none

Familial pituitary tumor syndrome 00:12:00

	Gene mutated	Clinical features
Multiple endocrine neoplasia 1 (MEN 1)	MEN 1 (11q13)	Hyperparathyroidism Pancreatic neuroendocrine tumors Foregut carcinoids

		Adrenal adenomas Skin lesions Pituitary adenomas (40%)
Multiple endocrine neoplasia 4 (MEN 4)	CDKNIB (12p13)	Hyperparathyroidism Pituitary adenomas Other tumors
Carney complex	PRKAR1A (17q23-24)	Pituitary hyperplasia and adenomas (10%) Atrial myxomas Schwannomas Adrenal hyperplasia Lentigines
Familial pituitary adenoma	AIP (11q.13.2)	Acromegaly/gigantism (~15% of afflicted families)

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Mc Cune Albright syndrome

↓

Polyostotic fibrous dysplasia

Prolactinomas

- Most common type pituitary adenoma – Prolactinoma[Q]
- Microprolactinomas: – F:M: – 20:1[Q]
- Macroprolactinomas: – F:M: – 1:1[Q]

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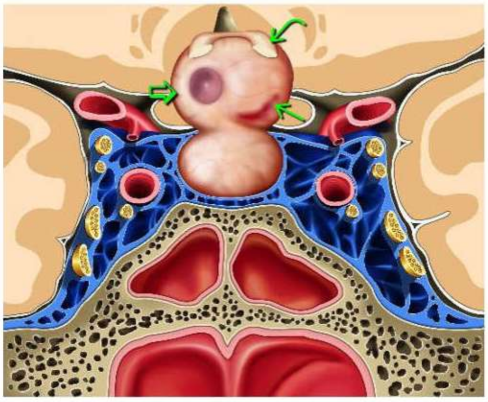

Fig: 4

Clinical features

- Females
  - Galactorrhea
  - Amenorrhea
  - Infertility
  - Loss of libido
- Male
  - Loss of libido
  - Impotence

- Decrease bone mineral density
- Decrease muscle mass
- Mass effect → Headache, visual disturbances

Investigations 00:18:31

- Fasting prolactin levels
  - Microprolactinoma >100µg/L
  - Macroprolactinoma >250µg/L
- MRI with gadolinium contrast

Treatment. 00:20:48

- Asymptomatic macroprolactinoma – wait & watch
- Symptomatic macroprolactinoma → Dopamine agonists
- Macroprolactinoma

Dopamine

ADR	
↓	1. Bromocriptine
Nausea	2. Cabergoline (DOC)
Vomiting	0.5-1mg twice weekly longer E ½
Postural hypotension	

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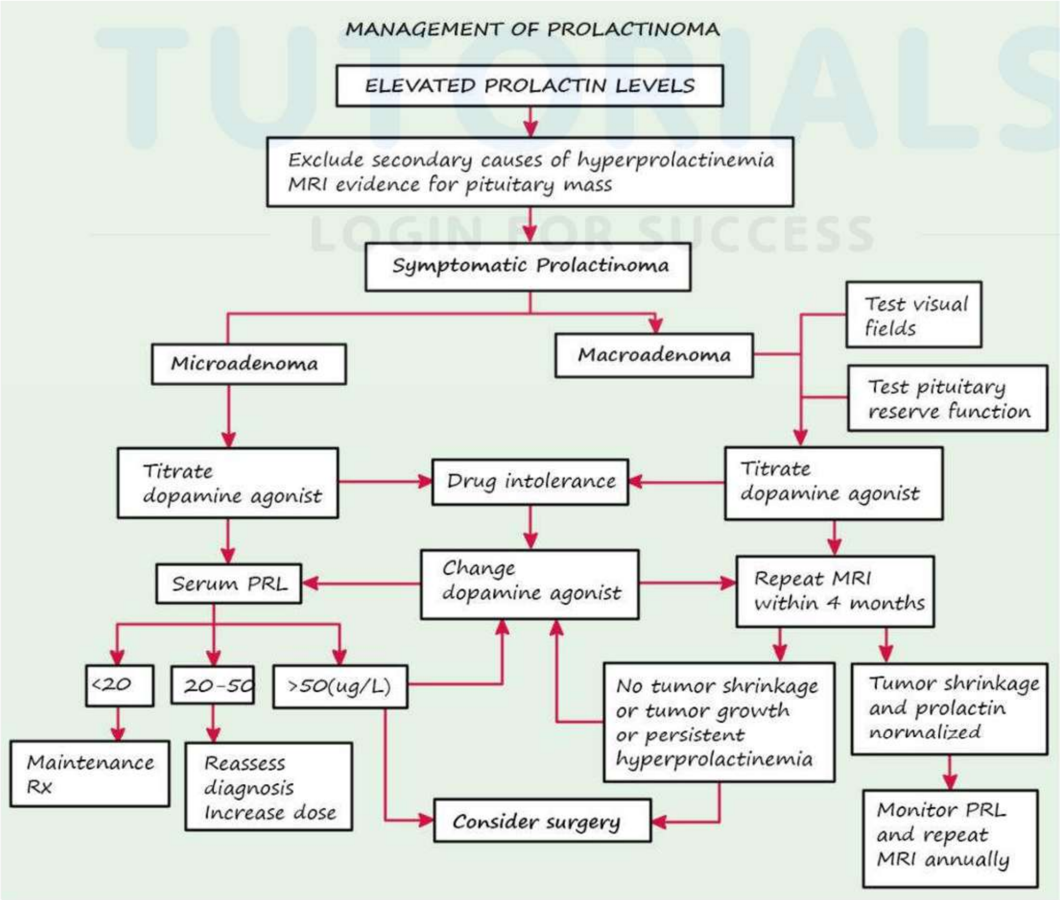

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Physiological conditions causing hyperprolactinemia

- Pregnancy
- Lactation
- Sleep
- Stress

Pathological conditions causing hyperprolactinemia

- Diseases affecting stalk
  - Lymphocytic hypophysis
  - Craniopharyngioma
- Pituitary tumors
  - Prolactinoma
  - Acromegaly
- Drugs induced
  - Typical antipsychotics – chlorpromazine
  - Atypical antipsychotic – risperidone
  - α methyl dopa
  - Metoclopramide
  - H_2 blockers – Ranitidine, cimetidine
  - Amitriptyline
- Systemic conditions
  - CRF
  - Hyperthyroidism

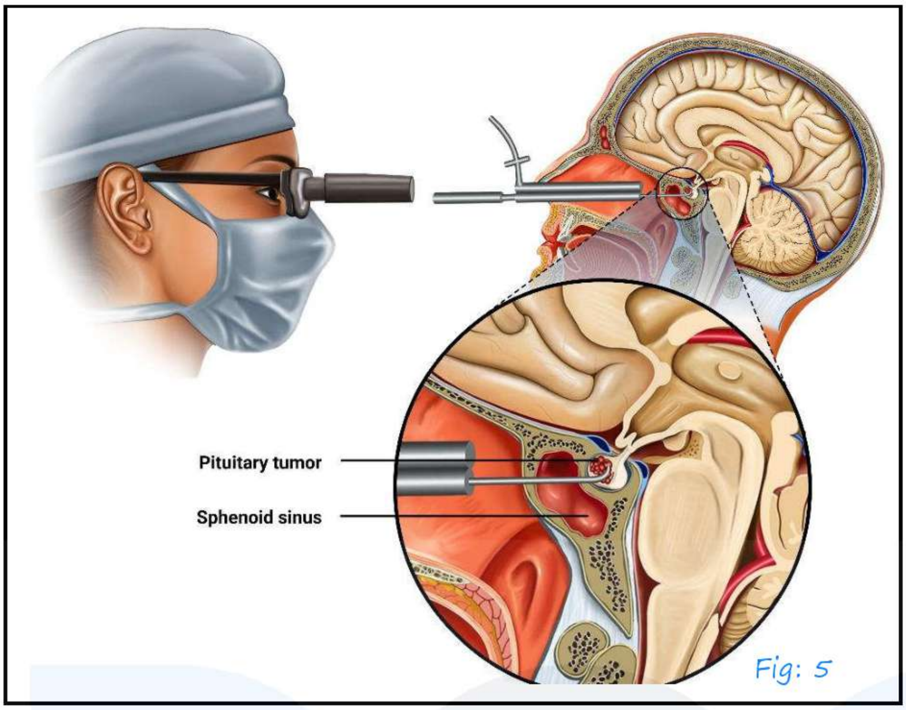

Fig: 5

- If surgery fails/patient not fit for surgery

  ↓

  Radiotherapy
- In pregnancy, lactotrope hyperplasia is likely to happen

  ↓

  Increase size of pituitary
- DOC of dopamine agonist in pregnancy – Bromocriptine

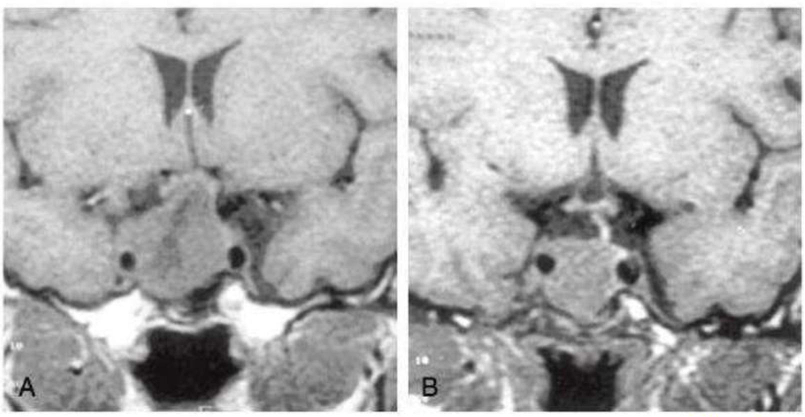

Fig: 6

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ACROMEGALY DIABITIES

Acromegaly 00:00:23

i. Condition in which GH is excess

ii. Gigantism → Before fusion of epiphysis

iii. Most common cause of acromegaly – GH producing pituitary adenoma (98%) → macroadenomas

iv. Acromegaly due to increases GHRH

↓

Central condition like hypothalamic hamartoma

Peripheral condition like ectopic GHRH

↓

Chest or abdominal carcinoid

Clinical manifestations

v. More in mates

vi. Increases GH, Increases IGF – I (somatomedin – c)

vii. Skin, viii. Organs, ix. Cartilage – May be involved

x. Soft tissue

Clinical Features

i. Facial features

ii. Organ

iii. Others

i. Facial Features

- Coarse facies
- Prominent supraorbital ride
- Frontal bossing
- Oily skin
- Large fleshy nose
- Thick lips
- Macroglossia
- Gap between incisors
- Jaw mal occlusion
- Prognathism

ii. Organ Involvement

↓

- CVS is prominently affected

↓

- Cardiomegaly
- Arrhythmias
- LVH
- Thyromegaly
- Increased risk of colonic polyps

↓

Colonic malignancy

iii. Others

- Hyperhidrosis
- Acanthosis nigricans
- Skin tags

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- Obstructive sleep apnea
- Husky voice

- 25% cases have diabetes mellitus
- Increases size of hands and feet
- Increases heel pad thickness

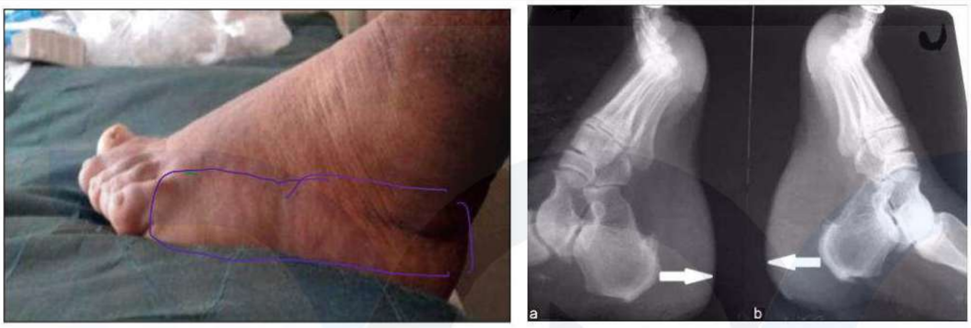

Fig: 1

Fig: 2

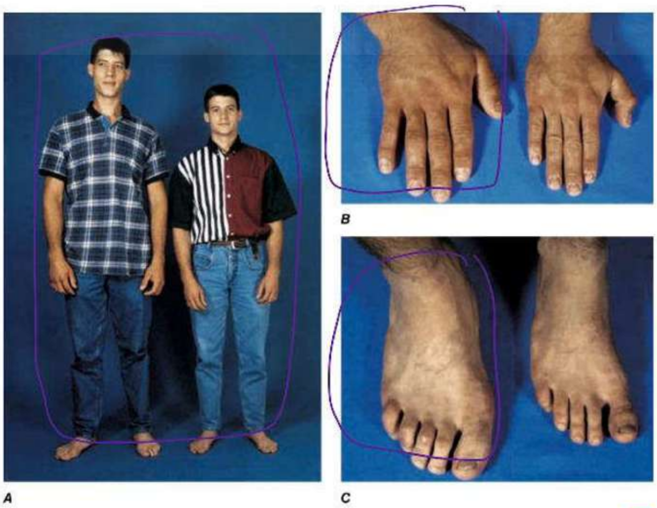

Fig: 3

Investigation 00:11:41

- Screening tests – Serum IGF – I level ↑↑
- Random Growth hormone assessment is completely wrong
- GH has pulsatile release, so random assessment would not be helpful
- Confirmatory test: Oral glucose GH suppression test

↓

TSg oral glucose → 1-2 hours → Gh < 0.4 μg/L

Treatment 00:15:30

- First choice – Surgery

↓

- Trans sphenoidal resection
- Microadenoma – 70% respond to surgery
- Macroadenoma - <50 % respond to surgery

↓

Check GH and IGF – I Levels

↓

High

↓

Re-surgery

Radiotherapy

Gamma knife radio surgery

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Drugs

- Somatostatin Analogues

  ↓

  - Laurentide
  - Octreotide

- GH receptors antagonist

  ↓

  Pegvisomant – daily SC injection

- Dopamine agonist

  ↓

  - Bromocriptine
  - Cabergoline

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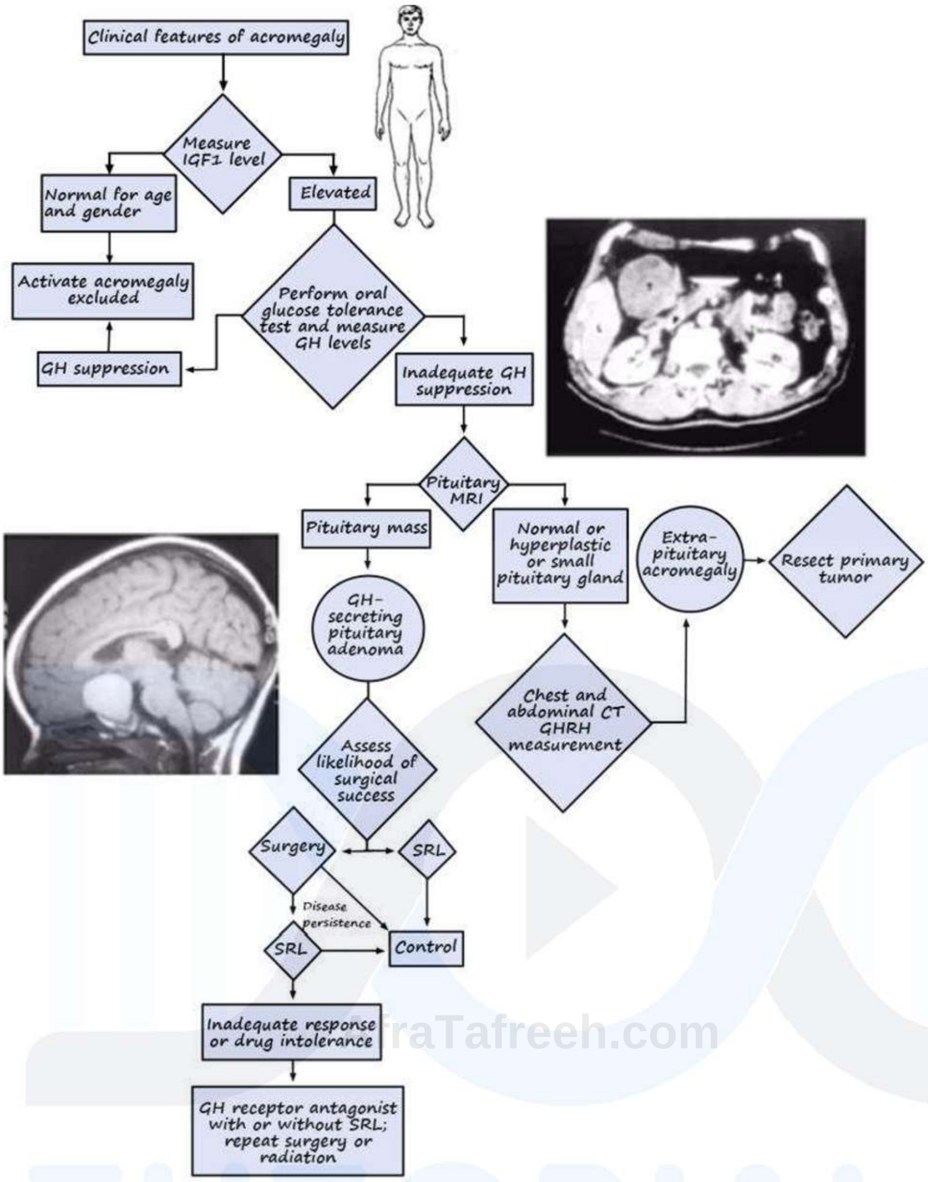

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NON-FUNCTIONAL TUMORS AND SUPRASELLAR TUMORS

25-35% of pituitary tumors

Most of them belong to gonadotrope category (FSH, LH)
(Clinical silent)

Non-functioning pituitary adenoma
↓
MRI differential diagnosis → Evaluate and manage as non-adenomatous sellar mass
↓
Assess pituitary function
↓
Non-functioning adenoma

- **Microadenoma**
  ↓
  Observe
  ↓
  Follow-up: MRI at 1,2 and 5years; reassess if symptomatic

- **Macroadenoma**
  ↓
  Transsphenoidal surgery
  ↓
  MRI
  Trophic hormone testing every 6months for 2years, annually thereafter, hormone replacement if required

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Fig: 1

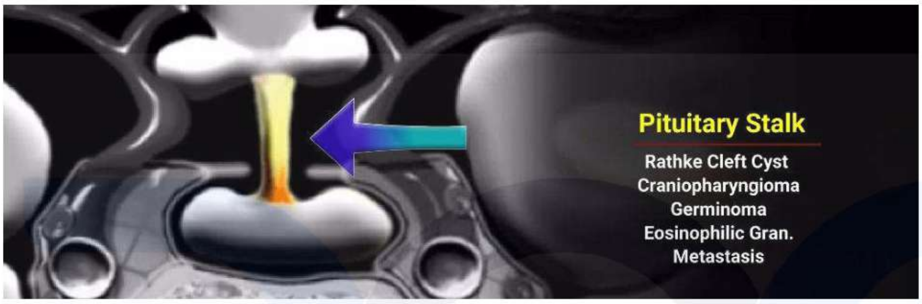

Fig: 2

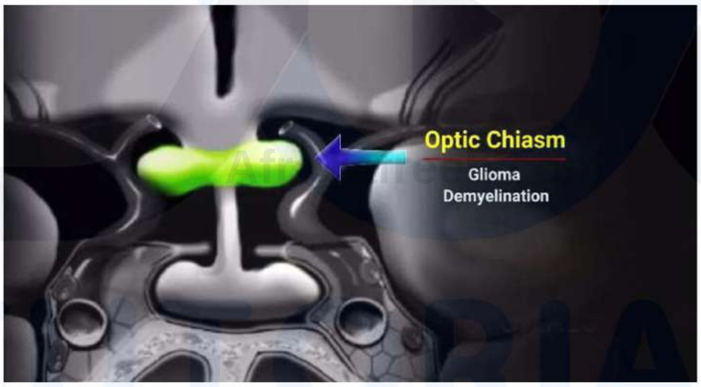

Fig: 3

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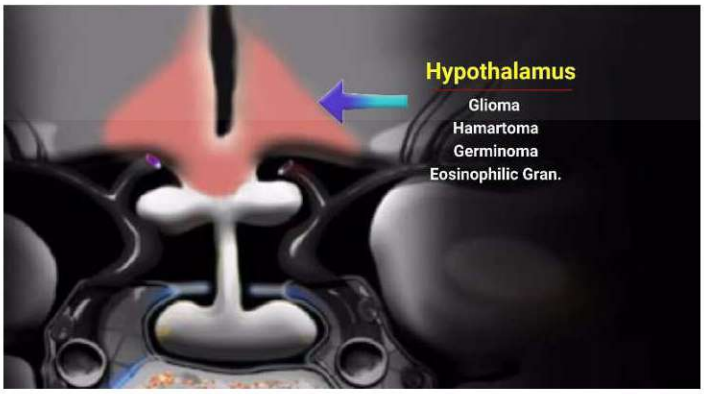

Fig: 4

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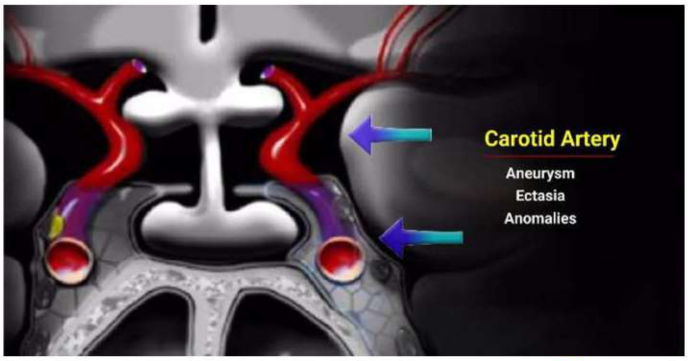

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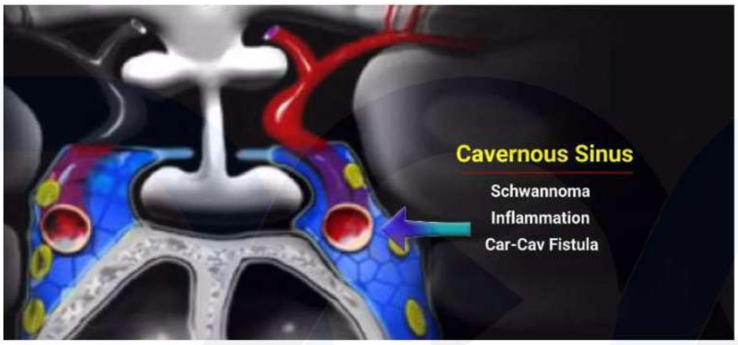

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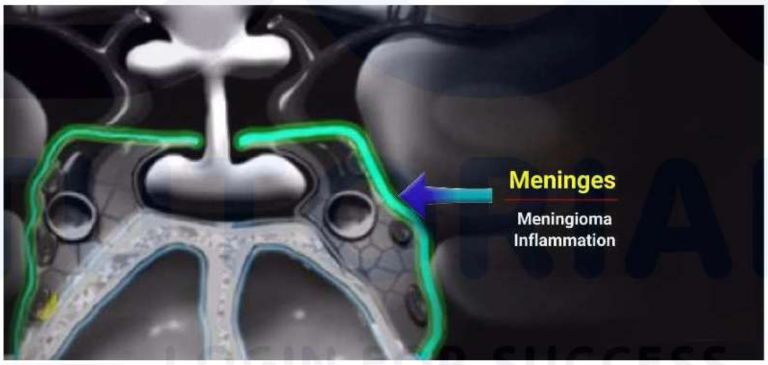

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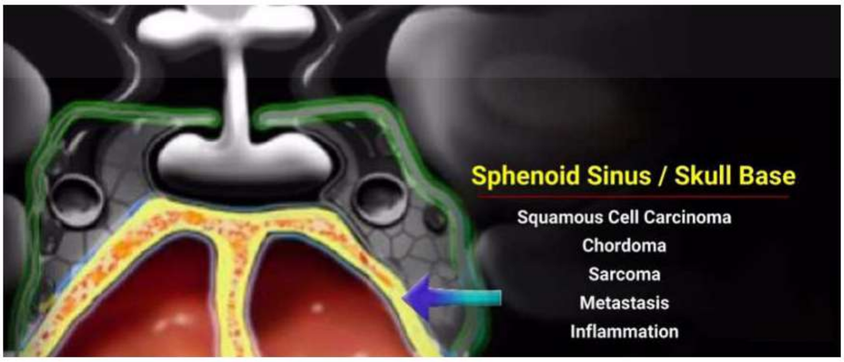

Fig: 8

Craniopharyngioma 00:07:17

- Benign lesion that originates from squamous remnants of rathke's pouch
- Mostly cystic → may be associated with calcifications
- Bimodal age distribution: 5-14years – childhood & adolescence
  - 50-74 years

Clinical features 00:08:50

- 60% → sellar
  - Hypopituitarism
  - Hyper-prolactinoma
  - Diabetes insipidus-10%
  - Headache
  - Visual field defects
- Imaging – CT/MRI

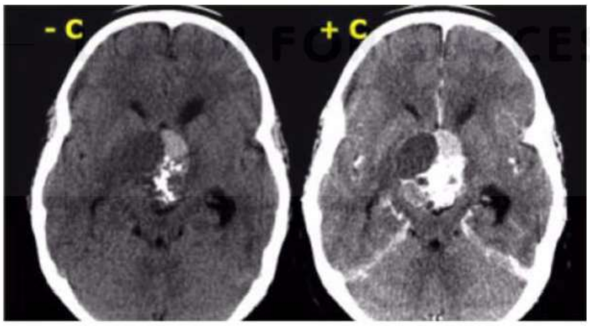

Fig: 9

- Mostly consists of cholesterol rich fluid

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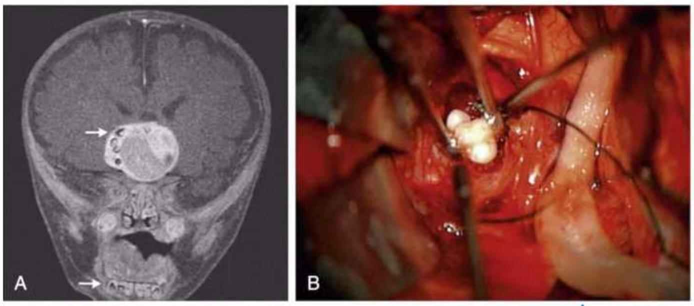

Fig: 10

- 2 histological subtypes
  - Adamantinomatous – aggressive
  - Papillary variant – less aggressive

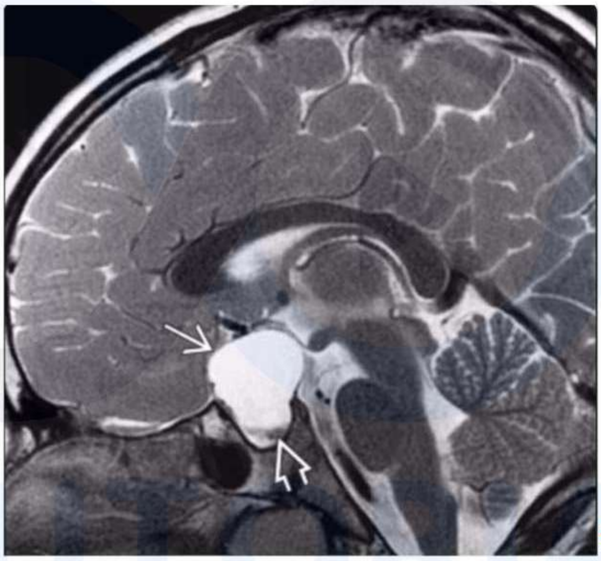

Fig: 11

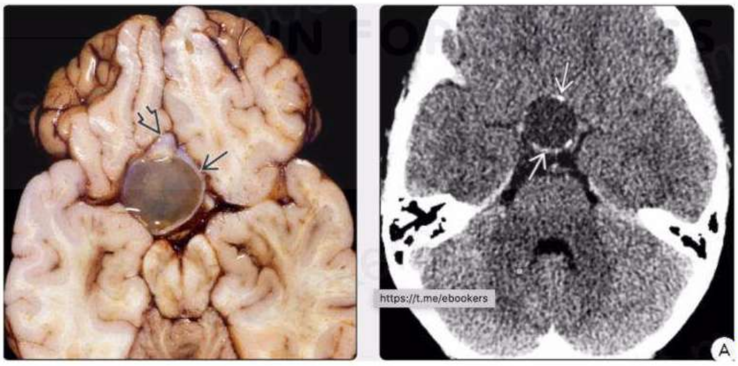

Fig: 12

Treatment

- Large lesions – surgery – trans-sphenoidal approach

- Sometimes – Radiotherapy
  - Both

Rathke's cleft cyst 00:16:52

- Occurs due to failure of involution of rathke's pouch
  - Cyst lined by squamous epithelium
- Clinical features
  - Hypopituitarism
  - Raised ICT features
- Age: - 45years
- Radiology: T_1 saggital contract sequence – claw sign

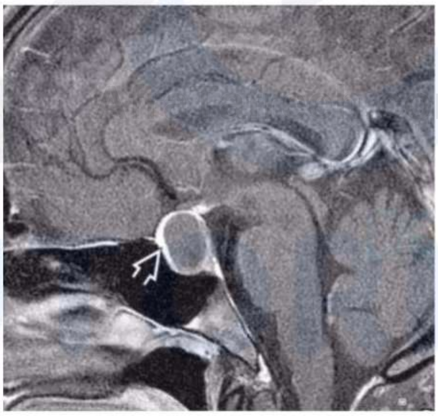

Fig: 13

- 40% sellar, rest suprasellar

Hypothalamic hamartoma 00:19:53

- Some may be from GnRH
  - Precocious puberty
  - Laughing associated seizure (Gelastic seizures)
- GHRH
- CRH

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Fig: 14

- Lesion lies between body & stalk

Other lesions

- Chordomas
- Meningiomas
- Pituitary mets.

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INTRODUCTION TO POSTERIOR PITUITARY

Disorders of neurohypophyses 00:00:35

- Hormones secreted by hypothalamus
- Supraoptic – ADH/Vasopressin/AVP
- Paraventricular – Oxytocin

↓

Milk let down

ADH. 00:02:16

- Antidiuretic hormone
- Secreted in hypothalamus and via axonal transport ADH stored in neurosecretory vesicles reaches post pituitary and released whenever needed by exocytosis

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Receptors of ADH 00:03:27

- V1 (V1a) → located in vascular smooth m/s platelets myometrium hepatocytes
- V1 → Located in renal tubules
- V3 (V1b) → Located in ant. pituitary → ACTH release
- Normal plasma osmolality → 285 – 290mosm/kg
- ADH α Plasma osmolality
- Osmoreceptor hub is in hypothalamus

↓

Function – Sensitive to plasma osmolality serum Na^+

$$\text{Serum osmolality} = 2\times s.\ Na^+ + \frac{\text{Blood sugar}}{18} + \frac{\text{BUN}}{2.8}$$

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- Thirst Centre is also located in hypothalamus

  ↓

  Set point is just above ADH
- So, we osmolality increase → ADH secretion increases → Thirst
- Adh release thirst → helps to maintain plasma osmolality in normal range

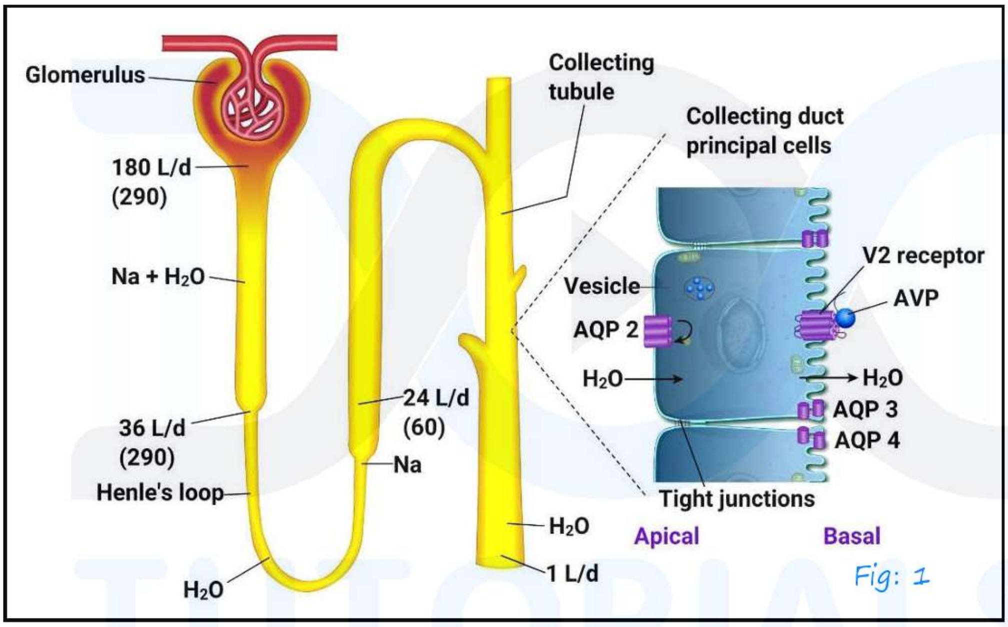

Fig: 1

- 80% filtrate – Reabsorbed in PCT
- Reabsorption that occurs in PCT is iso-osmotic reabsorption
- In Henle loop the plasma osmolarity of the filtrate increases when it reaches tip of Henle – Osmolarity in 1200 – 1400mosm/kg
- In ascending limb there is solute reabsorption
  By the time it reaches distal convoluted tubule

  ↓

  Osmolality is 60mosm/kg

- Concentration of urine →800-900mosm/kg (Urine osmolality)
- V2 receptor present in collecting tubule plays a role in concentrating urine

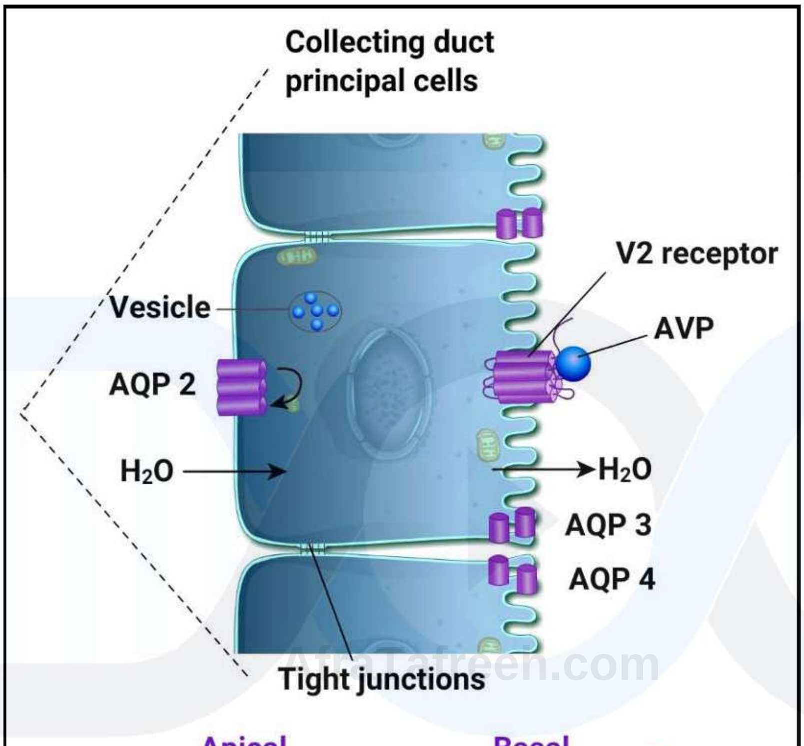

Fig: 2

- ADH binds to V2 receptors on the basolateral surface

  ↓

  Increase CAMP levels

  ↓

  Translocation of aquaporin 2 channel (Aqp2) (From vesicles transported to luminal side)

- Aquaporin 2 → Helps in reabsorption of water from filtrate
- In Basolateral side we have other channels → AQP3 & AQP4.

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SIADH

SIADH – Syndrome of inappropriate ADH secretion 00:00:25

- ADH α Plasma osmolality
- Hallmark: Low plasma osmolality
- Hypotonic hyponatremia – Increased plasma osmolality concurrent with decreases sodium

  ↓

  3 Forms

  1.Hypervolemic → CCSF, Cirrhosis

  2.Hypovolemic → Diarrhea, diuretic

  3.Euvolemic → SIADH
- Pseudo hyponatremia-increase lipids and proteins

Schwartz and Barrter criteria:

- Decrease plasma osmolality<275mosm/kg
- Urine osmolality >100mosm/kg
- Clinically euvolemic
- Increase ANP, RAAS inhibited
- Urine sodium >40meql/lit
- Normal thyroid,adrenal,renal and cardiac function.
- SIADH – Diagnosis of exclusion

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Etiology 00:10:06

Causes of Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

• Neoplasms • Carcinomas – Lung – Duodenum – Pancreas – Ovary – Bladder, ureter • Other neoplasms – Thymoma – Mesothelioma – Bronchial adenoma – Carcinoid – Gangliocytoma – Ewing's sarcoma • Head trauma (closed and penetrating infections – Pneumonia, bacterial or viral abscess, lung or brain – Cavitation (aspergillosis)	• Neurologic – Guillain Barre syndrome – Multiple sclerosis – Delirium tremens – Amyotrophic lateral sclerosis – Hydrocephalus – Psychosis – Peripheral neuropathy • Congenital malformations – Agenesis corps callosum – Cleft lip/palate – Other midline defects • Metabolic – Acute intermittent porphyria – Pulmonary – Asthma – Pneumothorax – Positive – pressure respiration • Drugs

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– Tuberculosis, lung or brain – Meningitis, bacterial or viral – Encephalitis – AIDS • Vascular – Cerebrovascular occlusions, – Hemorrhage – Cavernous sinus thrombosis	– Vasopressin or desmopressin – Serotonin reuptake inhibitors – Oxytocin, high dose – Vincristine – Carbamazepine – Nicotine – Phenothiazines – Cyclophosphamide – Tricyclic antidepressants – Monoamine oxidase inhibitors

Differential diagnosis

- SAH & head trauma – Cerebral salt wasting syndrome (CSWS)

↓

Mechanism

1.Impaired sympathetic neural input to kidneys

2.BNP

- Natriuresis/Salt wasting
- Polyuria
- Hypovolemic hyponatremia

Clinical Parameter	SIADH	Cerebral Salt Wasting
Serum sodium	Low	Low
Urine output	Normal or low	High
Urine sodium	High	Very high
Intravascular volume status	Normal or high	Low
Vasopressin level	High	Low

Treatment of SIADH 00:18:05

1.Fluid restriction → Chronic SIADH

↓

500ml less then 24hours urine volume

2.Vaptans – vasopressin receptor antagonist

↓

Selective V2 → tolvaptan (Orally) → DOC for SIADH

15mg → 30mg/60mg

V2 and V1a receptor antagonist → Conivaptan → Loading dose f/b infusion

↓

- Acute SIADH – Moderate to severe symptoms

3.Hypertonic saline (3% saline)

4.Demeclocycline – Acts by producing a state of nephrogenic diabetes insipidus

5.Fludrocortisone

- Patients with SIADH will have low serum uric acid.

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DIABETES INSIPIDUS DT

Diabetes insipidus DT 00:00:41

- Decrease production of ADH
- Decrease action of ADH

→ **Excessively dilute urine**

Polyuria (>40ml/kg)
3L/day
Polydipsia

- Divided into 2 types
  - i. Central
    - Cranial
    - Pituitary
    - Neurogenic
    - Neurohypophyseal
  - ii. Nephrogenic → defect in ADH action

Central D.I aetiology

i. Acquired

- Head injury
- Neoplasms
  - Craniopharyngioma
  - Pituitary adenoma
- Infections
  - Chronic meningitis
  - Viral encephalitis

- Toxoplasmosis
- Granulomatous lesions
  - Sarcoidosis
  - Histiocytosis X
- Vascular → aneurysm
- Congenital malformation
  - Septo-optic dysplasia
  - Midline craniofacial defects
- Genetic causes
  - AD
  - AR

- Gene affected in diabetes insipidus – AVP neurophysin II gene

Wolfram syndrome/ didmoad syndrome

- Diabetes insipidus
- Diabetes mellitus
- Optic atrophy
- Deafness

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Etiology of nephrogenic DI 00:08:28

Etiology of nephrogenic DI

- **Genetic**
- **Acquired**
  - **Infiltrative** → Amyloidosis
  - **Drugs** →
    - Lithium
    - Demeclocycline
    - Methoxyflurane
    - Amphotericin B
    - Rifampicin
    - Cisplatin
    - Foscarnet
  - **Metabolic** →
    - Hypercalcemia
    - Hypercalciuria
    - Hypokalaemia

Acquired

- **Granulomas** → Sarcoidosis
- **Neoplasms** → Sarcomas
- **Vascular** → Sickle cell d/s

Genetic causes

- **Autosomal dominant**
- **Autosomal recessive**
- **X-linked** → AVP receptor 2

Due to AGP_2 gene

Gestational diabetes insipidus

- Seen in 2nd and 3rd trimesters
- Placenta produces N-terminal amino-peptide

↓

Degrades AVP

Primary polydipsia

- Condition in which one consumes more water and in turn results in polyuria
- 2 types

i. Psychogenic
- OCO
- Schizophrenia

ii. Dipsogenic
- Infection (TB meningitis)
- Trauma
- Sarcoidosis

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Clinical features of DI

- Polyuria (nocturnal enuresis, increase frequency)
- Polydypsia
- Most important test to differentiate between polydypsia (psychogenic) and DI

↓

Water deprivation test

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Done in 2 phases

- **Dehydration phase**
- **Desmopressin phase**

Dehydration phase

- Certain baseline tests to be done
  - S. Na increase
  - S. osmolality increase
  - Urine osmolality decrease (<300 mosm/kg)
  - Weight
  - HR
  - BP
- Duration – 8hours (Patient should not take anything by mouth)
- For every 2 hours, measure
  - Urine osmolality
  - S. Na^+
  - S. osmolality

Situations – abort the test

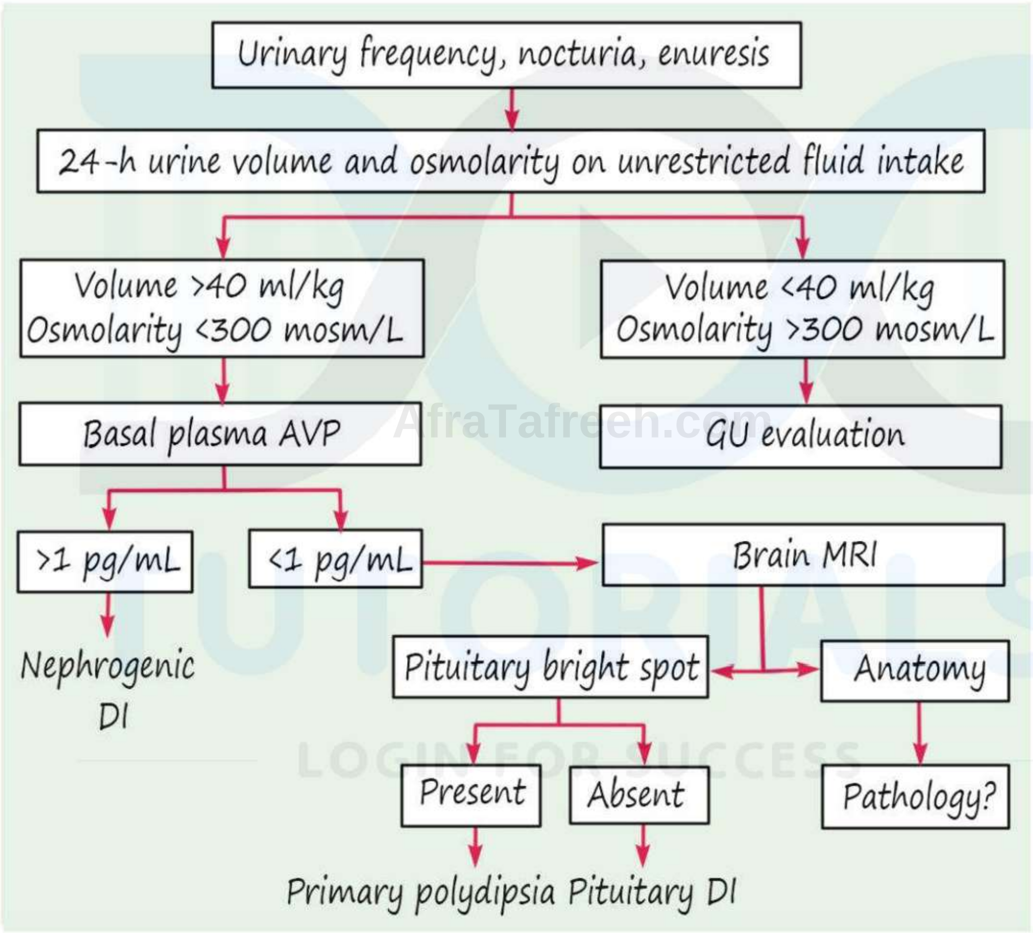
- >3% body weight is lost
- S. Na > 150 MEQ
- Inference

  i. Urine osmolality decrease → D.I

ii. Urine osmolality increase → psychogenic polydypsia

Desmopressin phase

- 2μg of decompression is given i.v or i.m
  - i. Urine osmolality increase (>50%) → central D.I
  - ii. Urine osmolality increase (5%) → nephrogenic DI



Treatment of DI 00:29:47

i. Central D.I

- Desmopressin (DOC)
  - Long half life
  - Oral

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- Sublingual
- S.C
- i.v
- Intranasal

ii. Partial central D.I

- Clofibrate
- Carbamazepine
- Chlorpropamide

iii. Nephrogenic D.I

- Thiazide diuretics (paradoxical action)
- Low salt diet
- Li induced DI – Amiloride (RNaC)

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INTRODUCTION TO THYROID GLAND

Disorders of thyroid gland 00:00:17

Basic of thyroid hormone synthesis

- Thyroid produces predominantly T_3, T_4
  - T_3 – Tri-iodothyronine
  - T_4 – Tetra

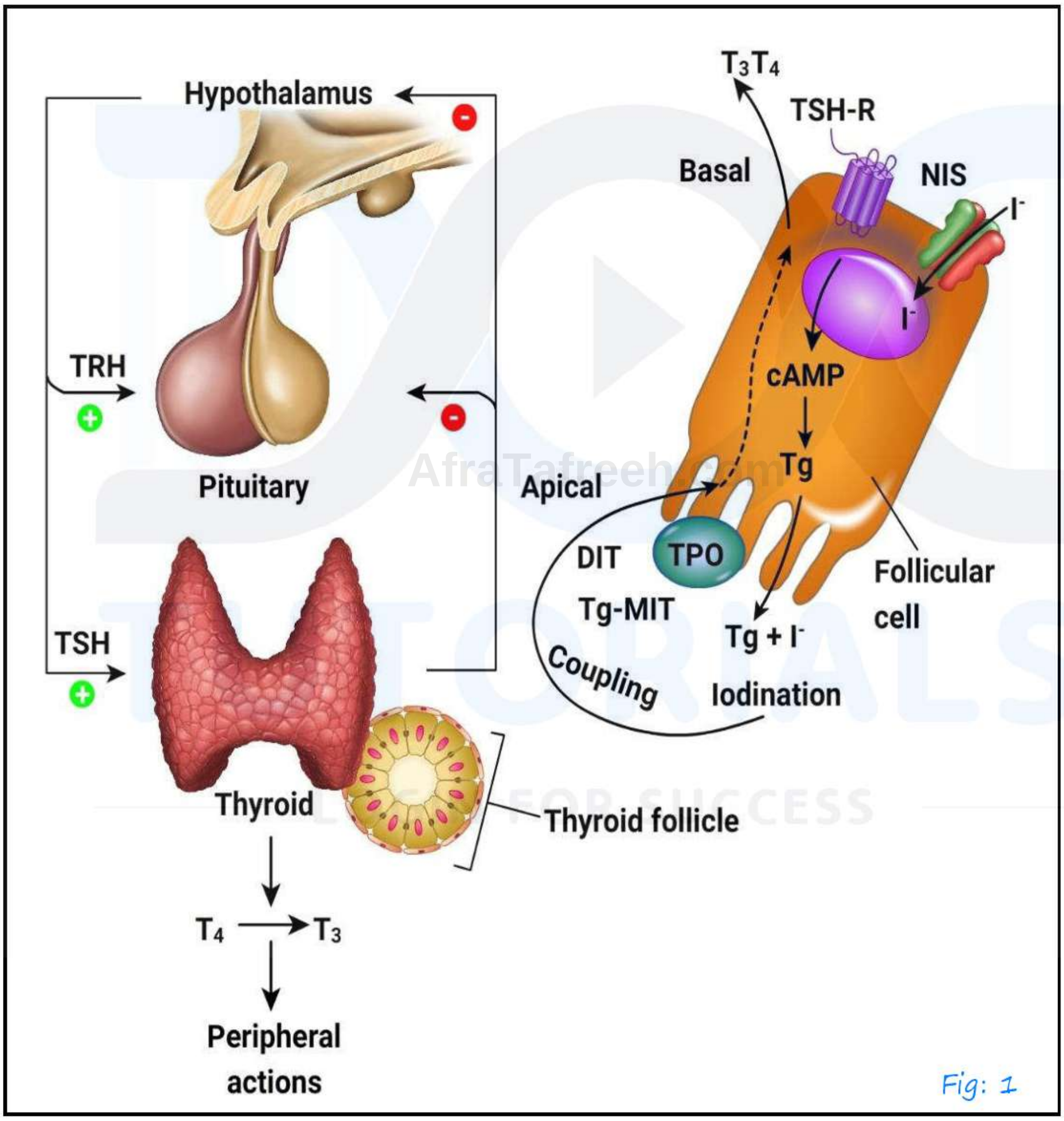

Fig: 1

Steps in thyroid hormone synthesis

i. Iodide trapping

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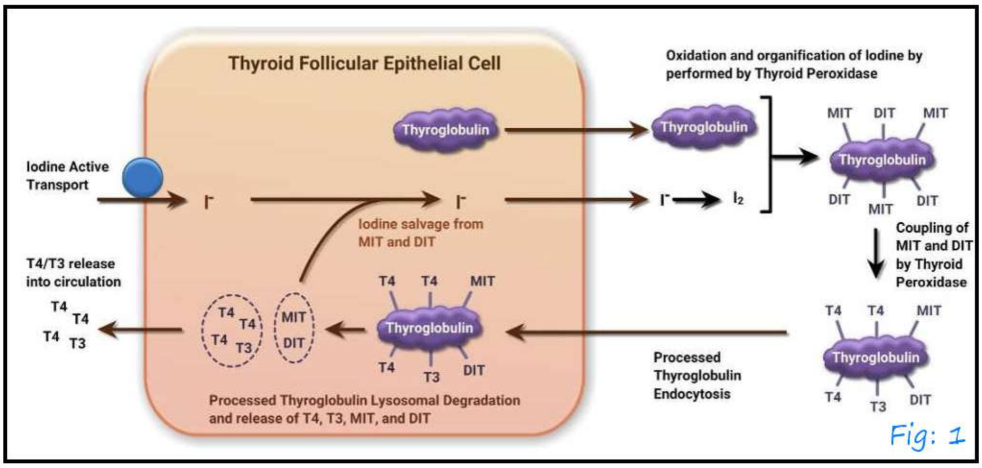

Fig: 1

- Iodine from blood enters thyroid follicular cell by Na^+I^- symporter

ii. Transport of I^- to follicular lumen

- Iodine goes through the apical side into lumen
- Coded by pendrin gene

↓

Mutation → Goiter, SNHL

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iii. Iodine oxidised to iodine (oxidation)

iv. Once TSH acts on TSH receptor inducing the formation of cAMP and subsequently thyroglobin formation

↓

Thyroglobulin comes to luminal side

↓

Thyroglobulin has lots of tyrosine residues

↓

Iodine formed binds to tyrosine residues of thyroglobulin resulting in formation of MIT, DIT, etc.

↓

Organifiction

v. Coupling

- $MIT + DIT \rightarrow T_3$
- $DIT + DIT \rightarrow T_4$

- Oxidation
- Organification
- Coupling

] **mediated by enzyme thyroid peroxidase**

vi. Endocytosis

- By endocytosis, the thyroglobulin complex is taken inside and all these residues are released and subsequently get access to peripheral lumen

vii. Release of T_3, T_4

$$T_4 \xrightarrow{S^1 - \text{deiodinase}} T_3 \text{ (more potent)}$$

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- 20% of T_3 produced form thyroid
- 80% of T_3 produced by De-iodination of T_4
  - T ½ of T_4 – 7 days
  - T ½ of T_3 – 12 days

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BASIS OF THYROID FUNCTION TEST

Basics of Thyroid function test 00:00:24

- Estimation of TSH, T_3, T_4

Estimation of TSH

- Previously, there were 1st generation assay

↓ 2nd generation assay

Low values of TSH could not be picked up

↓

3rd generation assays – can pick low values

We can do either total T_3 or T_4, but the problem with T_3 and T_4 is protein binding

↓

Conditions altering protein binding will interfere in estimation of T_3, T_4

↓

estimation of free T_3 and free T_4 is preferred

- Thyroid binding globulin may be increased in
  - Pregnancy
  - OCP
  - Hormone therapy
  - Tamoxifen
  - SERM's

↓

- Increase total T_3, T_4

- TBG decreased in
  - Nephrotic syndrome
  - Androgens

  } **Decrease total T_3, T_4**

- Certain drugs like
  - Phenytoin
  - CBZ

  } **Also interfere with protein binding**

  - NSAID's

Primary hypothyroidism

- Problem lies in thyroid gland
- Thyroid gland is not able to produce sufficient amount of T_3, T_4
  - TSH production as there is no feedback inhibition

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Secondary hypothyroidism

- Thyroid gland is normal
- Problem in pituitary, TSH is not produced in adequate amount
- In some scenarios, T_3 & T_4 decreased, TSH is normal

↓

Inappropriately Ⓝ TSH in 2°

	T_3	T_4	T_5
Primary hypothyroidism	↓	↓	↓
Secondary hypothyroidism	↓	↓	↓

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Grave's disease

- Overproduction of T_3 and T_4, TSH definitely supressed because of feedback inhibition
- TSH secreting adenoma of anterior pituitary

	T_3	T_4	T_5
Grave's disease	↑	↑	↓↓↓
Secondary hypothyroidism	↑	↑	↑↑↑
Resistance to thyroid hormone	↑	↑	↑↑

- Hashimoto thyroiditis
- Grave's disease

} **Autoimmune origin**

↓

Antibodies are tested

↓

i. Anti TPO
ii. Anti-thyroglobulin

} **Elevated in Hashimoto's &**

iii. Anti TSH receptor

Other investigations

- Radioactive iodine uptake → differentiates not and cold nodule
  - I^{123}, I^{132}, Tc^{99} used
- Thyroid ultrasound – to know the echo structure
- FNAC – tissue diagnosis

HYPOTHYROIDISM

Etiology 00:00:21

1. Autoimmune
2. Iodine deficiency
3. Congenital
4. Drugs induced
   - Antithyroid
   - Lithium
   - Amiodarone
   - Interferon – α
   - Sunitinib

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Clinical features:

- Congenital hypothyroidism
  - Prolonged jaundice
  - Macroglossia
  - Hypotonia
  - Poor feeding
  - Delayed bone development

(All of the above) → If not treated early → Neurological sequent → Mental retardation

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Fig: 1

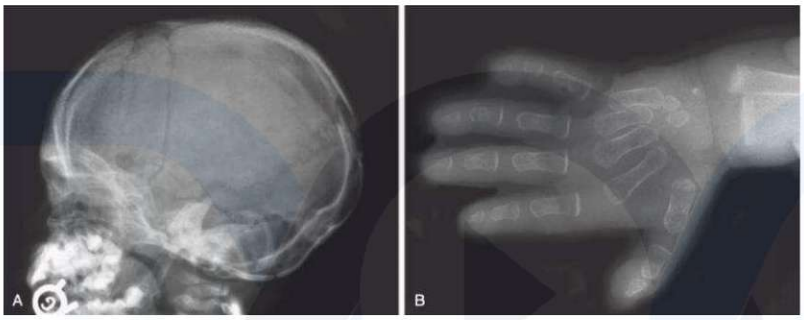

Fig: 2

Adult hypothyroidism

Signs and symptoms of hypothyroidism (Descending order of frequency)	
Symptoms	**Signs**
Tiredness, Weakness	Dry coarse skin: cool peripheral
Dry skin	Extremities
Feeling cold	Puffy face, hand and feet (Myxedema)
Hair loss	Diffuse alopecia
Difficulty concentrating and poor memory	Bradycardia
Constipation	Peripheral edema
Weight gain with poor appetite	Delayed tendon reflex relaxation
Dyspnea	

Hoarse voice Menorrhagia (Later oligomenorrhea or amenorrhea) Paresthesia Impaired hearing	Carpal tunnel syndrome Serous cavity effusions

Fig: 3

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- CVS → Decreased myocardial contractility
- Non pitting edema
- T3, T4 are needed for removal of glycosaminoglycans
- In hypothyroidism there is defective clearance of GAG's

  ↓

  GAG accumulate → Imbibe water
- Delayed relaxation of ankle jerk

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Hashimoto's thyroiditis

- Autoimmune
- As known as lymphocytic thyroiditis
- Pathogenesis involves
- Environmental factors
- Host factors
- Genetic factors
- F > M
- Mean age: 40-60yrs
- Characterized by lymphocytic infiltration of thyroid gland
- Among genetics → HCA DR polymorphism, CTLA4 polymorphism, HLA DR 3,4,5 } X
- Down's syndrome
- Turner's syndrome
- Antibodies associated are Anti TPO & Anti thyroglobulin
- 20% pts may have anti TSH receptor antibodies

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Clinical features

- Goiter → Irregular firm enlargement
- At time of lymphangitic phase
- ↑TSH, T3 & T4 → Normal → Stage of subclinical hypothyroidism

↓

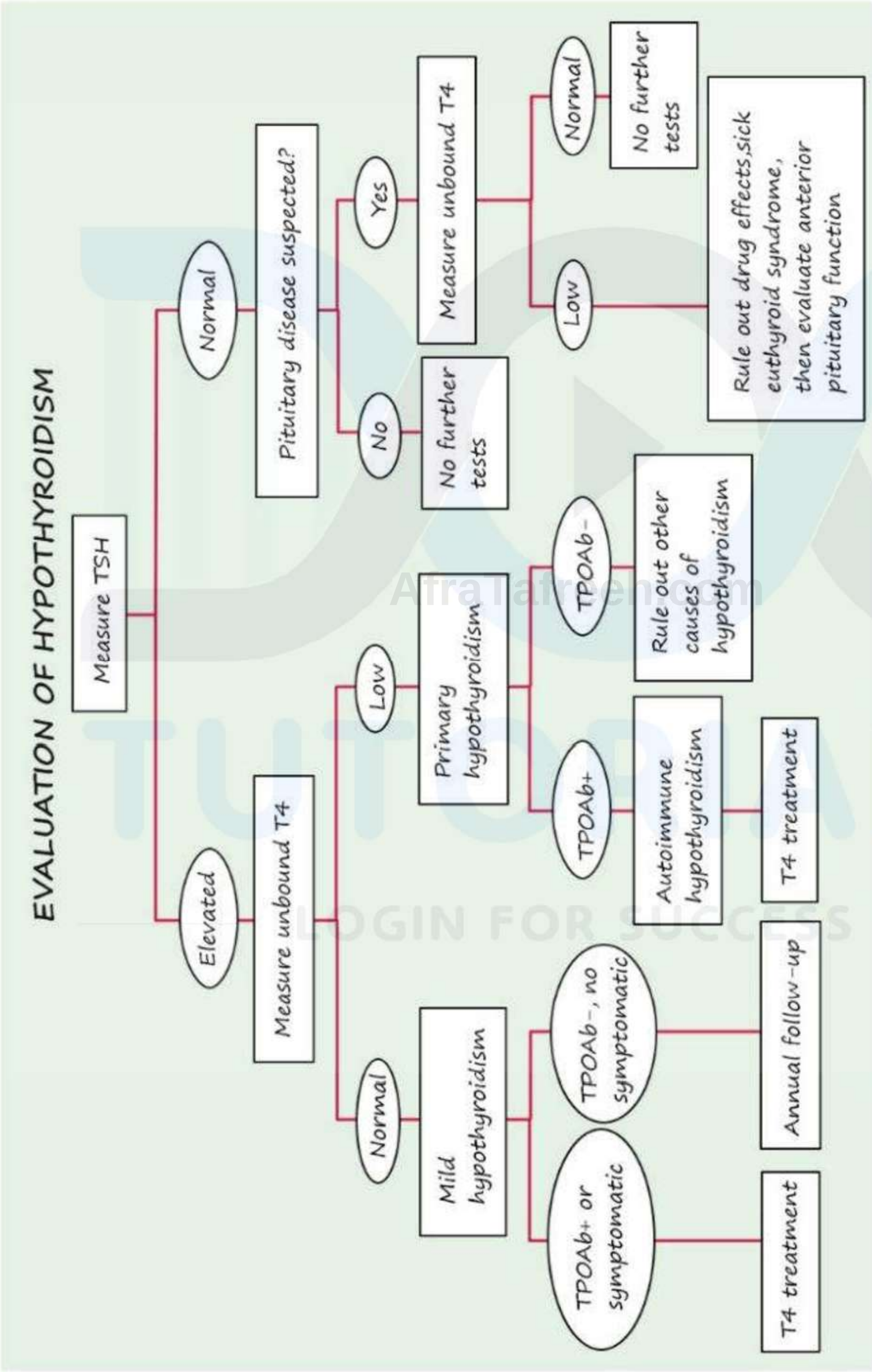
TSH 5-10MIU/L

- Later it goes to atrophic stage

↓

- Features of overt hypothyroidism or clinical hypothyroidism develop

Work up a case of hypothyroidism



- Normal TSH rules out 1° hypothyroidisms

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Treatment of hypothyroidism 00:29:45

- Levothyroxine (T4)
  - Oral tablets
  - Empty stomach
  - 30min before breakfast
  - 1.6 – 1.8mg/kg body weight

    ↓

    50/75mg tablets
- In elderly patients
- If started on 50mg → Takes 8 –10weeks for TSH to reach optimal range (Normal value – 0.5 – 5 MIU/L)

$$T4 \xrightarrow{5^{1} \text{ deiodinases}} 3$$

- Ensure good drug compliance
- T1/2 T4 – 7days → So no problem if dose is missed one day

Myxedema coma 00:43:09

- Result of untreated hypothyroidism
- Endocrine emergency
- Common in elderly age group
- Triggers
- Infection like pneumonia
- MI
- Stroke
- CCF
- Drugs - sedatives antidepressants

Clinical features

- Symptoms of hypothyroidism
- Decreases level of consciousness
- Stupor/COMA
- Seizures
- Hypothermia
- Hyperventilation → Hypoxia & Hypercapnia
- Hyponatremia
- Hypoglycemia

Treatment

- Endocrine emergency
- Treatment thyroid hormone deficiency + Correcting physiology imbalances

  1.IV supplementation of thyroid hormone

  ↓

  IV levothyroxine (T4) + IV Liothyronine (T3)

  NG tube → T4 tablets → Effects is not good as there will be decreased GI absorption

  2.Parenteral steroids

  ↓

  Hydrocortisone 50mg 6th hourly

  3.Fluid and electrolytic imbalance

  ↓

  Hypertonic saline

  Hypoglycemia corrected

  4.Repeat ABG

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5.Blankets to avoid heat loss

6.Treatment any precipitating cause

- Mortality is best setting: 20-40%

Hashimoto encephalitis

- As known as SREAT → Steroid responsive encephalopathy associated with autoimmune thyroiditis
- Presents with features of encephalopathy movement disorder → Myoclonus tremor
- Associated with Anti TPO & Anti thyroglobulin
- Treatment: Dramatically steroid responsive

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THYROTOXICOSIS

Thyrotoxicosis. 00:00:43

- Thyrotoxicosis → increase T_3 & T_4
- All cases of thyrotoxicosis need not be accompanied by Hyperthyroidism.
- Hyperthyroidism → thyrotoxicosis

- Etiology of thyrotoxicosis

  1.1° Hyperthyroidism

  a)Grave's d/s (most common) -60-80%

  b)Toxic multinodular goitre

  c)Toxic adenoma

  d) Iodine excess (Jod Basedow phenomenon)

  2.Thyrotoxicosis not associated with hyperthyroidism

  ↓

  Subacute thyroiditis

  Silent thyroiditis

  Thyrotoxicosis factitia → increased exogenous thyroxine

  3.Secondary Hyperthyroidism

  ↓

  TSH secreting pituitary adenoma

Grave's disease.

- Autoimmune condition
- Hyper functional thyroid gland

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- F > M
- 20-50 years
- Etiopathogenesis → Genetic factors

  Host factors

  Environmental factors

  Genetic factors → HLA DR polymorphisms → HLA B_8

  CTLA 4 polymorphisms

Other Contributary factors

1. Smoking
2. Post-partum
3. stress
4. Reconstitution phase of HAART
5. Alemtuzumab Rp

- Gland is hyper functional because of Thyroid Stimulating immunoglobulins (TS1)
- Antibodies
  - Anti TPO
  - Anti TG
  - Anti TSH-R

  (Anti TPO, Anti TG, Anti TSH-R: 80% cases)
- Thyroid ophthalmopathy

  ↓

  Infiltration by T cells → release of cytokines (TNF, IL-1)

  ↓

  Accumulation of GAG

  ↓

Imbibe water

↓

Ophthalmopathy → proptosis diplopia

Clinical features. 00:14:08

- Symptoms
- Weight loss (weight gain in 10% of patients)
- Palpitations
- Dyspnea
- Tremor
- Tiredness, fatigue, muscle weakness
- Heat intolerance, increased sweating
- Increased stool frequency
- Anxiety, altered mood, insomnia
- Nervousness, hyperactivity
- Pruritus
- Thirst and polyuria
- Menstrual disturbances in women (oligomenorrhea or amenorrhea)
- Loss of libido
- Neck fullness
- Eye symptoms (swelling, pain, redness, double vision)

- Symptoms

  1.paroxysmal palpitation

  2.dyspnea due to volume overload

  3.fine tremor

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4.Hypokalemic paralysis

- Signs
  - Physical signs of hyperthyroidism
  - Tachycardia, atrial fibrillation
  - Systolic hypertension, increased pulse pressure
  - Cardiac failure
  - Weight loss
  - Fine tremor, hyperkinesis, hyperreflexia
  - Warm, moist skin
  - Palmar erythema and onycholysis
  - Muscle weakness
  - Hair loss
  - Diffuse, palpable goitre and thyroid bruit
  - Mental-status and mood changes (eg, mania or depression)
- Commonest ECG finding – Sinus Tachycardia
- Bounding pulse
- Neuronal hyperexcitability
- Elderly patient with depression – Apathetic thyrotoxicosis
  - Extrathyroidal physical signs
    - Eyelid lag, retraction or both
    - Proptosis (exophthalmos)
    - Double vision (extraocular-muscle dysfuntion)
    - Periorbital edema, chemosis, scleral injection
    - Exposure keratitis
    - Optic neuropathy

- Localized dermopathy
- Acropachy

- Dermopathy
  - Pre tibial myxoedema (< 5%)
  - pink / purple induration over anterior and lateral leg
- Acropachy → clubbing (< 1%)

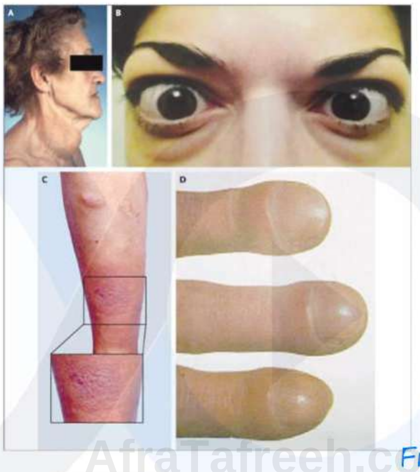

Fig: 1

Clinical manifestation of specific causes of thyrotoxicosis	
Clinical findings	Causes
Diffuse goitres	Grave's disease, silent thyroiditis's
Unimodular goitre	Thyroid autonomy
Multinodular goitre	Thyroid autonomy
Impalpable thyroid gland	Exogenous thyroid hormone
Thyroid pain and tenderises	Subacute thyroidits
Ophthalmopathy	Grave's disease

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Localized demonopathy	Grave's disease
Thyroid acropachy	Grave's disease

Thyroid Ophthalmopathy

- Lid retraction due to sympathetic overactivity
- Proptosis staring look – Kocher's Sign

Fig: 2

Darlymple's sign – Lid retraction

Joffroy's Sign – absence of wrinkles on looking above mobius sign – convergence is defective

Fig: 3

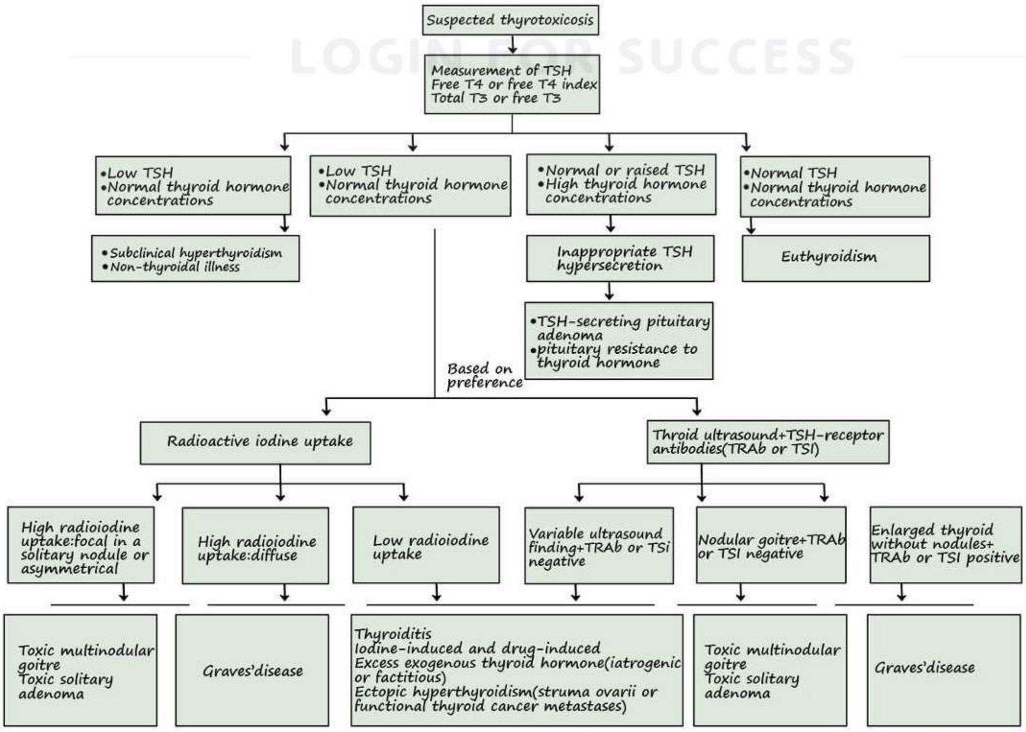
Right lid lag on downgaze – von Graefe sign

Stellwags sign – infrequent eye blinking

No specs Scoring System

Class	Description
0	No physical signs or symptoms
1	Only signs, no symptoms (example, upper lid retraction, stare, and eyelid lag) Soft tissue involvement (symptoms and signs) 23456 Sight loss (optc nerve involvement)
2	Soft tissue involvement (symptoms and sign)
3	Proptosis
4	Extraocular muscle involvement
5	Corneal involvement
6	Sight loos (optic nerve involvement)

Evaluation of thyrotoxicosis



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- 1° Hyperthyroidism → increase T_4, increase T_3

  ↓↓ TSH

- 2° Hyperthyroidism→ increase T_4, increase T_3

  Increase TSH

- 2 –5 % cases of thyrotoxicosis may have T_3 toxicosis

  ↓

  Increase T_3, Normal T_4

  ↓↓ TSH

Treatment of thyrotoxicosis

1.Antithyroid drugs

2.Radio – Iodine

3.Surgery

Antithyroid drugs

1.Thioamides → Propylthiouracil, Carbimazole, Methimazole } act by perpendicular TPO [Q]

- Propyl thiouracil perpendicular S^1 deiodinase

  ↓

  T_4 → T_3

- PTU

  1.100-200 mg Q 6H/Q8H

  2.t ½ -90 mins

  3.S/E – Hepatotoxicity

4.Doc in pregnancy (1st trimester)

↓

Highly plasma protein bound drug

↓

Does not easily cross placenta (not teratogenic)

5.DOC in thyrotoxic crisis

- Carbimazole / Methimazole
- Teratogenic – not given in 1st trimester
- Given in 2nd & 3rd trimester
- 10-20 mg Q8H /Q12 H
- S/E: - Cholestasis
- S/E of thioamides → rash

    Arthralgia

    Agranulocytosis → fever, sore

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Fig: 4

Features of methimazole embryopathy

- aplasia cutis
- choanal atresia
- TE fistula

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2.Beta blockers → Propranolol → decrease sympathetic overdrive

→ perpendicular conversion of $T_4 \rightarrow T_3$

Radia iodine

- 1st is used
- Cause damage to follicular epithelial cells and thereby interfere with productions of hormone synthesis.
- Pre-treatment with antithyroid drugs for 1 month before radioactive iodine therapy
- Inadequate preparation leads to thyrotoxic crisis
- C/I – Pregnancy
  Lactation
- Used as caution in thyroid ophthalmopathy (mod – severe)
- Commonly used when there is relapse following antithyroid treatment

Clinical conditions that favour a particular treatment modality for graves hyperthyroidism			
Condition	**A TD**	**RAI**	**Surgery**
High chance of remission	+		
Active Graves orbitopathy	+		
Elderly with comorbidities	+	+	
Increased surgical risk	+	+	

Liver disease		+	
Major adverse reactions ATD		+	
Hypokalemic periodic paralysis		+	
Pulmonary hypertension or congestive heart failure		+	
Previous neck surgery or irradiation		+	
Recurrent hyperthyroidism		+	+
Malignancy suspected			+
Large thyroid nodules			+
Coexistent hyperparathyroidism			+

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Follow up

- Free T_4 is monitored after 4-6 weeks
- Dose titration

Thyrotoxic Crisis

- Alkla thyroid storm
- Triggers

a) Infections like pneumonia, sepsis

b) Cardiovascular accidents

c) Cerebrovascular accidents

d) Radio iodine therapy without pre-treatment with antithyroid drugs

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- C/F
  a) Fever
  b) Altered sensorium → Coma
  c) Seizures
  d) Vomiting
  e) Diarrhoea
  f) Jaundice

Treatment → Endocrine emergency

1. Propylthiouracil
   a) 500 mg-1000mg loading dose followed by 250 mg Q4H
   b) Either orally / Ryles tube
2. Iodide: 1 hour after PTU loading dose wolf chaikof effect: iodide has the property of inhibiting thyroid hormone
3. Beta blockers: -
   a) Decrease sympathetic overdrive
   b) Perpendicular conversion of T_4 → T_3
   c) Propranolol 60mg orally Q4H
   d) I V esmolol may be tried
4. Steroids
   a) Parenteral hydrocortisone
      300mg → 100 mg Q8H
5. IV Fluids
6. O_2 support
7. Correct any electrolyte imbalance

Thyrotoxicosis without hyperthyroidism

Thyrotoxicosis without hyperthyroidism
Subacute thyroiditis
Silent thyroiditis
Other causes of thyroid destruction: amiodarone, radiation, infarction of adenoma
Ingestion of excess thyroid (Thyrotoxicosis factitia) or thyroid tissue

- Struma ovari – Ectopic tissue producing thyroid hormone S/O ovarian teratoma

Thyroiditis. 01:13:55

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1.Some inflammation in thyroid gland

2.May be

Acute subacute chronic

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3.Causes: -

Causes of Thyroiditis
Acute
Bacterial infection: especially Staphylococcus, Streptococcus, and Enterobacter Fungal infection: Aspergillus, Candida, Coccidioides, Histoplasma, and
Pneumocystis
Radiation thyroiditis after treatment

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Amiodarone (may also be subacute or chronic)
Subacute
Viral (or granulomatous) thyroiditis
Silent thyroiditis (including postpartum thyroiditis
Mycobacterial infection
Drug induced (interferon, amiodarone)
Chronic
Autoimmunity: focal thyroiditis, Hashimoto's thyroiditis, atrophic thyroiditis
Riedel's thyroiditis
Parasitic thyroiditis: echinococcosis, strongyloidiasis, cysticertosis
Traumatic: after palpation

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Features of Acute thyroiditis

- Painful thyroid swelling
- Fever
- Sore throat
- Tender thyroid
- ESR increase
- TFT- Normal

Treatment:

- Antibiotics
- Abscess drainage

VIRAL THYROIDITIS/GRANULOMATOUS THYROIDITIS

(De Quervain's thyroiditis)

- Most common in females (F>M-3:1)
- Age group: 30-50 years
- Virus
  - a) Mumps
  - b) Coxsackie
  - c) Adenovirus
  - d) Influenza
- 3 phases
  - a) Thyrotoxic phase → painful thyroid swelling
    - sore throat
    - fever
    - tender thyroid
    - increase ESR
    - increase FT_3, increase FT_4
    - decrease TSH

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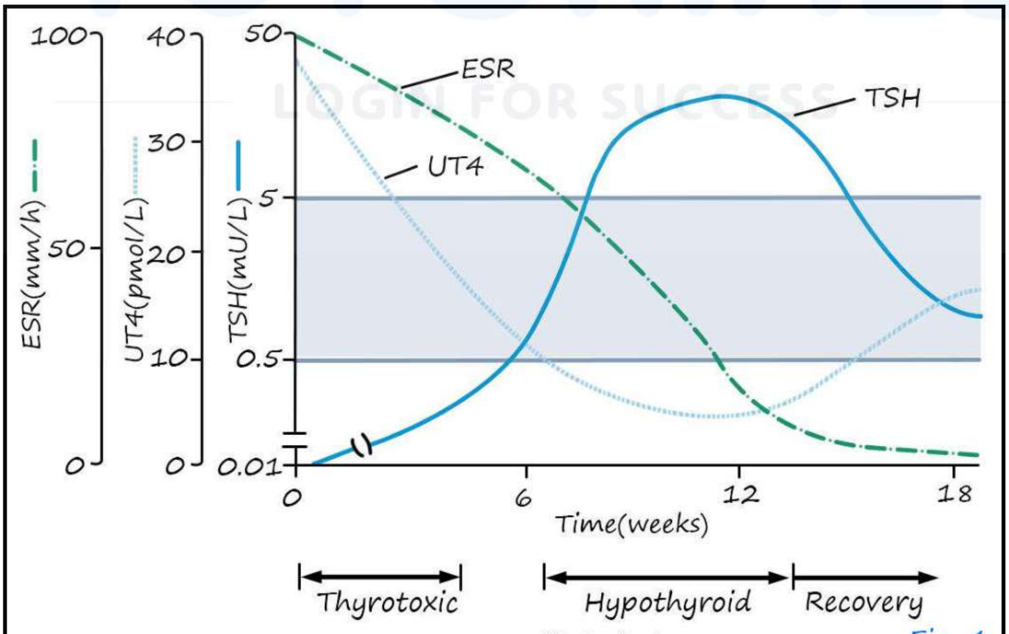

Fig: 4

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b) Hypothyroid phase → decrease FT_3, decrease FT_4, increase TSH

c) Recovery phase → Normal T_3, T_4, TSH
Normal ESR

RAIU

- I^{123} Uptake decreased in viral thyroiditis
- Grave's d/s -BIL diffuse increased uptake

Treatment:

- Aspirin booms 4-6 hourly
- NSAID'S
- Glucocorticoids – 6-8 weeks
- Beta blockers
- No role for antithyroid drug
- Levothyroxine – supplemented in viral thyroiditis only if hypothyroid phase is prolonged

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Silent thyroiditis

- Painters' thyroiditis
- 3 phases
  a) Thyrotoxic
  b) Hypothyroid
  c) Recovery
- ESR – Normal
- RAIU – Decreased
- Treatment – Glucocorticoids not useful

- Levothyroxine – supplemented only if hypothyroid phase is prolonged

Sick euthyroid state (SES)

- Also referred to as Non thyroidal illness (NTI)
- Increase IL-6 → alters TFT

↓

Low T_3 levels (both free & total)

↓

Normal T_4 & TSH

Effect of amiodarone on thyroid function

- Amiodarone – class III anti-arrhythmic

↓

- 39% by weight → Iodine
- Distributed in body fat
- Con produce
  a)Hypothyroidism
  b)Thyrotoxicosis
- Hypothyroidism
  a)Acute transient→ wolf chai off effect
  b)Prolonged → inhibition of 5^1 deiodinase
- Thyrotoxicosis
  a)AIT Type I
  b)AIT Type II

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AIT – Type I	AIT Type II
Jod Basedow effect	Lysosomal activation ↓ Destructive thyroiditis

Differences between amiodarone – induced thyrotoxicosis type 1 and type 2		
	AIT Type 1	AIT Type 2
Underlying thyroid abnormality	Yes	no
Onset after start amio darone	Short (3 months)	Long (30 months)
Thyroid antibodies	Present in graves	Usally absent
Colour flow doppler sonography	Low, normal, high	Suppressed
Preferred treatment	Antithyroid drugs	Oral prednisone
Amiodarone continuation	No	Possible

Spontaneous remission	No	Frequent
Subsequent hypothyroidism	No	Possible (17%)
Subsequent definitive treatment	Generally, yes	No

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INTRODUCTION AND HYPERPARATHYROIDISM

Disorders of parathyroid gland 00:00:21

- Parathyroid glands are located adjacent to thyroid gland

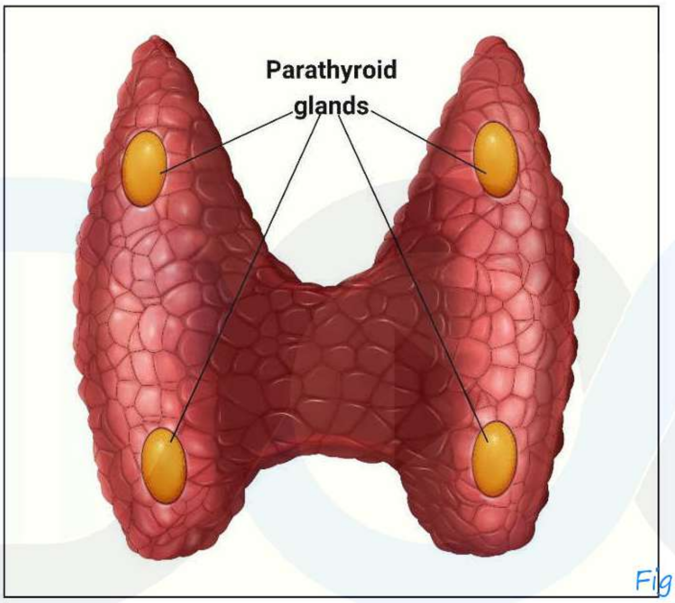

Fig: 1

- Pair of superior parathyroid glands
  - Inferior parathyroid glands

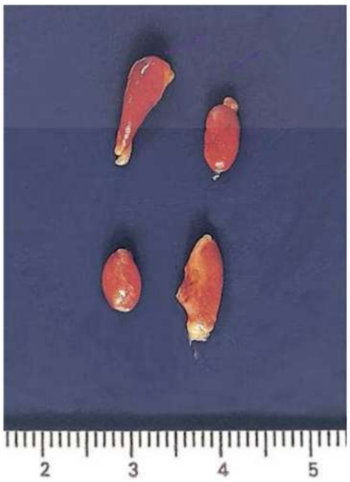

Fig: 2

- Hormone produced - PTH

PTH

- Has 84 amino acids
- Most important regulator for PTH secretion – S.calcium
- Calcium sensing receptor is located in parathyroid gland which can sense the level of extracellular calcium and subsequently adjust the secretion of parathormone

↓Plasma calcium

↓

Parathyroid glands

↑Parathyroid hormone

↓

↑Plasma parathyroid hormone

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Kidneys

- ↑Calcium reabsorption → ↓Urinary excretion of calcium
- ↑1,25-$(OH)_2D_3$ formation → ↑Plasma ↑1,25-$(OH)_2D_3$ → Intestine ↑Calcium absorption

Bone

- ↑Resorption → ↑Release of calcium into plasma

↓

Restoration of plasma calcium toward normal

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Action of PTH on kidney

- It acts on distal tubules resulting in increased calcium reabsorption
- Acts on proximal tubules and cause increase in phosphate excretion
- PTH would stimulate 1α hydroxylase and results in active vitamin D formation
- Activated vitamin D is responsible for Ca^{2+} from bones absorption from intestine

Action of PTH on bones

- PTH would cause resorption of Ca^{2+} from bones and resulting in increased level of plasma Ca^{2+}
- Initially activate the osteoclast → resorption of Ca^{2+}

  ↓

  ↑level of plasma Ca^{2+}
- Induce osteoblast
  - Increase bone turn over
  - Increase ALP

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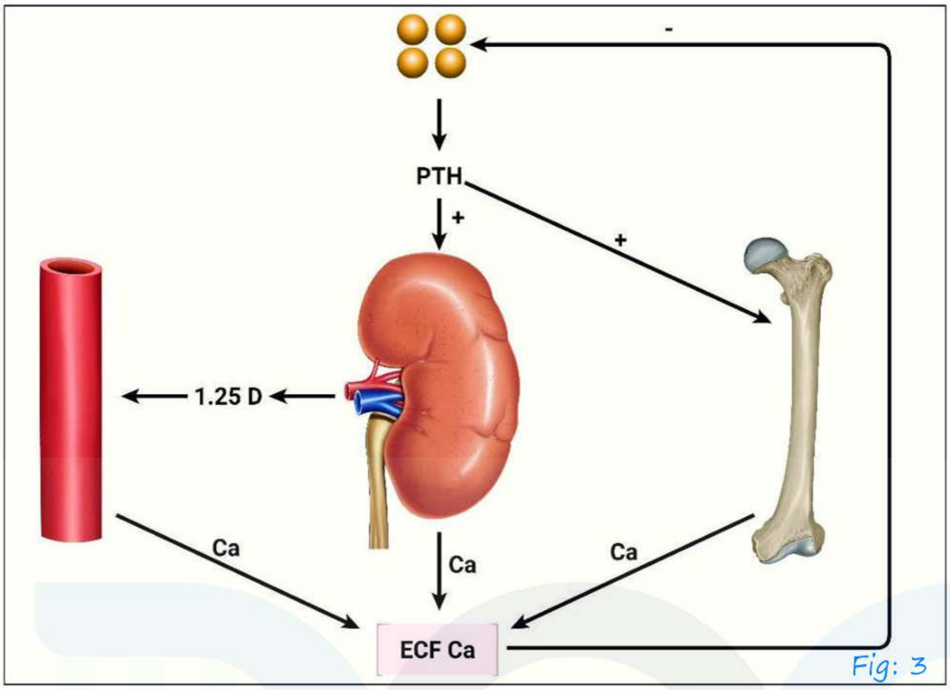

Fig: 3

- Normal calcium level: 9-11mg/dL

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Hyperparathyroidism

Classification

- 1° → 1° problem in parathyroid gland → ↑PTH
- 2° → ↓Ca^{2+} → ↑PTH
- 3° → Rare Chronic Hyperparathyroidism → Hypertrophy of parathyroid gland

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Primary hyperparathyroidism 00:12:10

Etiology

- 80% – parathyroid adenoma
- 15% – diffuse parathyroid hyperplasia
- Parathyroid carcinoma

Part of syndromes

- MEN 1
- MEN 2
- Hyperparathyroidism jaw tumor syndrome

Clinical features

- Kidney
  - Recurrent nephrolithiasis

    ↓

    Calcium oxalate, calcium phosphate stones

    Results in UTI
  - Nephrocalcinosis
- Bone → subperiosteal bone resorption (early)

  ↓

  Phalanges
- Osteitis fibrosa cystica

  ↓

  Happens due to

  i. Osteoclast activation

  ii. Osteoblastic activity

  - Bone pain ⊕

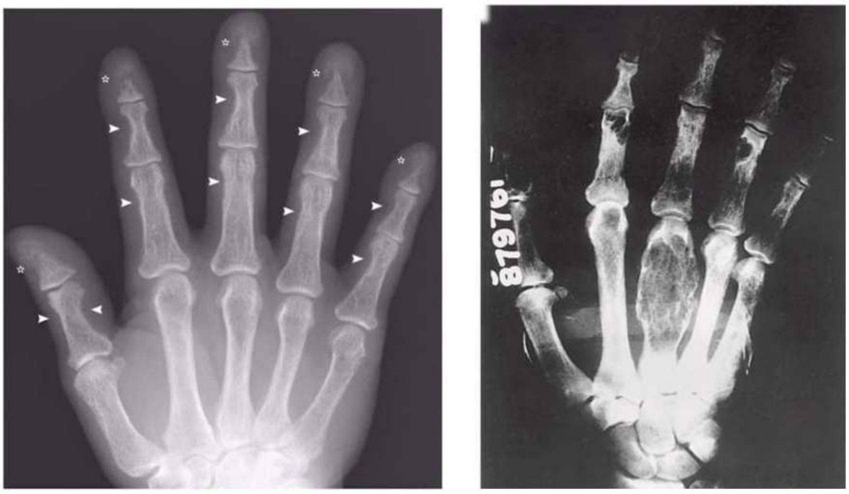

Fig: 4

- In some cases, osteoblastomas – brown tumors of hyperparathyroidism may be present

Salt & pepper skull Fig: 5

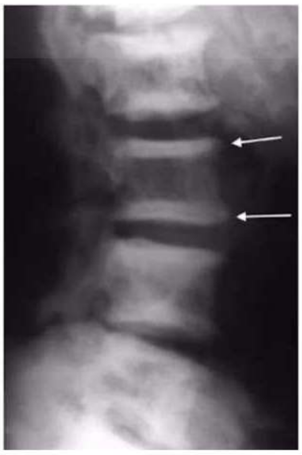

Fig: 6

Rugger jersy spine

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- GIT → Abdominal pain
- Psychiatric manifestations
  - Bones, stones, groans, moans

Cardiovascular

- Hypertension
- Ventricular arrythmias
- ECG[1] changes (shortened QT interval, [2]widened T wave)

Renal

- Polyuria
- Impaired renal concentrating ability
- Kidney stones
- Hyperchloremic metabolic acidosis
- Dehydration
- Polydipsia
- Kidney failure

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Gastrointestinal

- Constipation
- Nausea and vomiting
- Anorexia
- Pancreatitis
- Peptic ulcer disease

Musculoskeletal

- Muscle weakness
- Osteoporosis

Neurological

- Mental status change (example: delirium, psychosis, coma)

Investigations

- S.Ca^{2+} increase
- S.Po_4^{3-} decrease
- S.PTH increase
- ALP increase
- Localisation → Technitium sestamibi scan

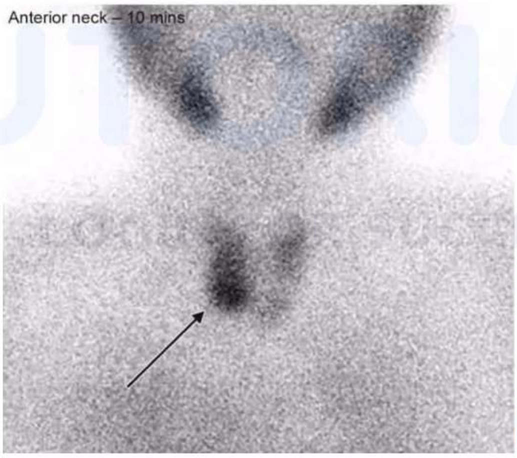

Fig: 7

Treatment

- Adenoma -80% - Surgery
- Hyperplasia -15% - Near total parathyroidectomy (3½ glands removed)

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Indications of surgery

- Overt clinical manifestations of disease
  - Kidney stones (or) nephrocalcinosis
  - Fractures (or) classic radiographic findings of osteitis fibrosa
  - Classic neuromuscular disease
  - Symptomatic (or) life-threatening hypercalcemia
- Serum calcium >1 mg/dL above upper limit of normal
- Creatinine clearance <60mL/min, presence of stone(s) by radiograph, CT, (or) ultrasound
- Urinary calcium >400mg/day plus other urinary biochemical indices of stone risk
- Bone mineral density low (T score ≤-2.5) at any site[a]
- Presence of vertebral fracture by radiograph (or) by vertebral fracture analysis on DXA
- History of fragility fracture
- Young age (<50years)
- Uncertain prospects for adequate medical monitoring
- If patient has florid symptoms of hypercalcemia

↓

Treatment hypercalcemia before surgery

Hypercalcemia treatment

- Fluid supplementation → Normal saline

- Furosemide → Increase urinary Ca^{2+} excretion
- Bisphosphonates → DOC
- Calcitonin → Inhibit osteoclastic activity
- Denosumab → targets RANKL
- Glucocorticoids

Type of therapy	Usual dose	Frequency
Rehydration	2-4L/day of 0.9% NaCl IV	qd x 1-5days
Furosemide	20-40mg IV (after rehydration)	q12-24hours
Pamidronate	60-90mg IV over 2-4hours	Once
Zoledronate	4mg IV over 15-30min	Once
Denosumab	60mg SC	Weekly
Calcitonin	4-8IU/kg SC	q12-24hours
Gallium nitrate	200mg/m² IV over 24hours	qd x 5days
Glucocorticoids	200-300mg hydrocortisone IV 40-60mg prednisone PO	qd x 3-5days qd x 3-5days

- Secondary hyperparathyroidism
- Tertiary hyperparathyroidism

(both) → CKD

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HYPOPARATHYROIDISM

Hypoparathyroidism	00:00:16

Hypoparathyroidism
- True
- pseudo

Hypoparathyroidism

- Decrease production of hormone from parathyroid glands (decrease PTH)
- Etiology

Causes on hypoparathyroidism
Genetic disorders
Abnormal parathyroid gland development
Abnormal PTH synthesis
Activating mutation of calcium-sensing receptor (autosomal dominant hypocalcemia or sporadic isolated hypoparathyroidism)
Post-surgical (thyroidectomy, parathyroidectomy, radical neck dissection)
Autoimmune
Autoimmune polyglandular syndrome (associated with chronic mucocutaneous candidiasis and primary adrenal insufficiency)

Isolated hypoparathyroidism due to activating antibodies to calcium-sensing receptor
Infiltration of the parathyroid gland (granulomatous, iron overload, metastases)
Radiation-induced destruction parathyroid glands
Hungry bone syndrome (post parathyroidectomy)
HIV infection

- Features of hungry bone syndrome
  - Hypocalcemia
  - Hypophosphatemia
  - Hypomagnesemia
- Clinical features

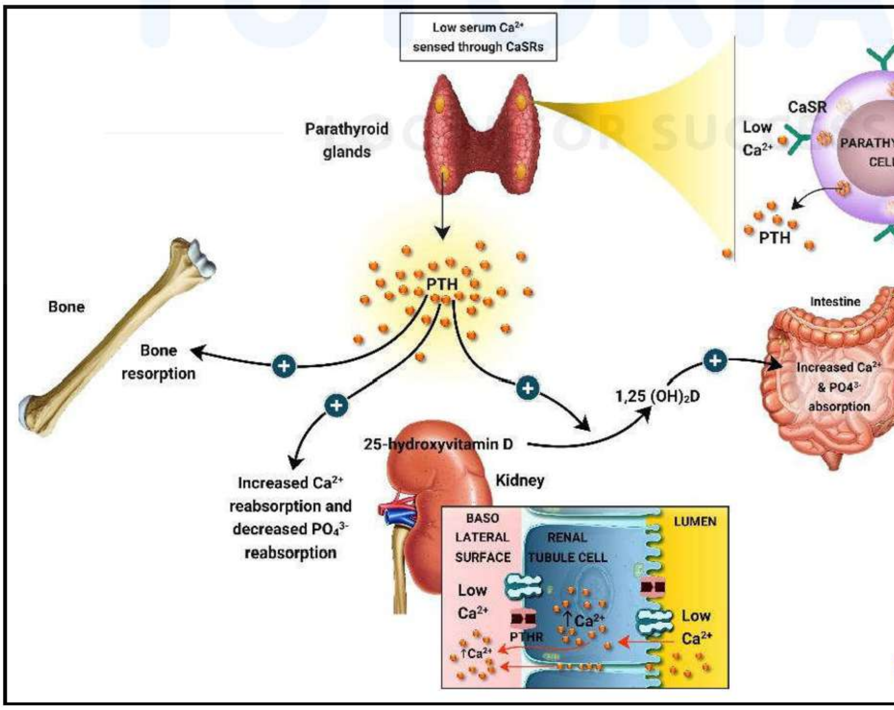

Fig: 1

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- Most of the dominant features are due to hypocalcemia

Acute — chronic

Clinical manifestations of hypocalcemia
Acute
Neuromuscular irritability (Tetany)
Paresthesias (peri-oral, extremities)
Muscle twitching
Carapopedal spasm
Trousseau's sign
Chvostek's sign
Seizures
Laryngospasm
Bronchospasm
Cardiac
Prolonged QT interval
Hypotension
Heart failure

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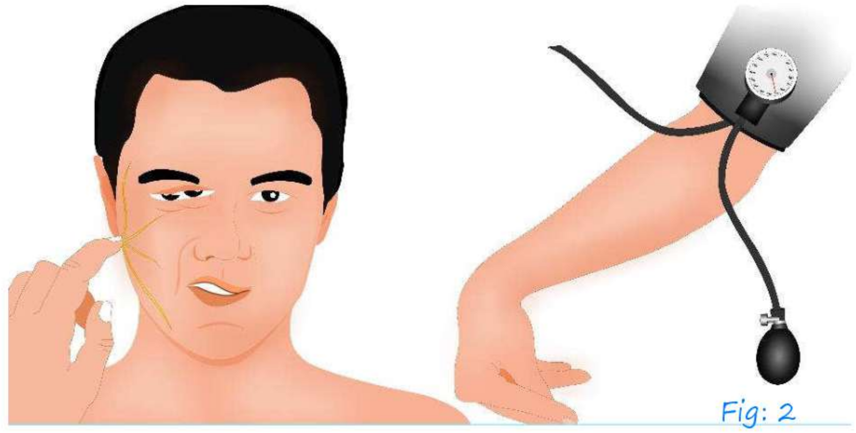

Fig: 2

- Chvostek's sign

↓

When you tap the anterior border of parotid, that is where your facial nerve is exciting

↓

Because of increased excitability of facial nerve

↓

Muscle twitching

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- Trousseau sign/obstetrician's hand

↓

BP cuff is tied and pressure is elevated 20 mmHg above systolic BP and hold it for 3 minutes

↓

Carpopedal spasm

Fig: 3

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Investigations

- Decrease Ca^{2+}
- Increase Po_4^{3-}
- S. Alkaline phosphate – normal

Treatment:

- Acute symptomatic hypocalcemia

  ↓

  i.v calcium gluconate (10ml 10% calcium gluconate

  over 5–10 mins)

  followed by

  calcium gluconate infusion (10–24g) over 24 hours

  as infusion-in dextrose/ normal saline

  – Oral calcium 2g/day

  – Activated vitamin D
- Chronic hypokalemia

  – Oral calcium

  – Activated vitamin D.

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PSEUDOHYPOPARATHYROIDISM

Pseudohypoparathyroidism: 00:00:12

- Actual problem is resistance to PTH

  ↓

  S. Ca low

  S. PO_4^{3-} ↑

  S. PTH ↑

- Heterogenous group of disorders

Types
- Type → Complete PTH
  - 1a → GS α mutation → Component of adenylate adenylate cyclase enzyme → Certain skeletal 2 Developmental ab (N) present
  - 1b → Absent
- Type 2 → Partial PTH resistance

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- Skeletal change – AHO (Albrights hereditary osteodystrophy)
- Short 4th metacarpal > Metatarsal

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- Obesity
- Round face
- Mental sub normality

Fig: 1

Pseudo Pseudohypoparathyroidism:

- Subtype
- Almost similar to type 1a with exception that the biochemical parameters would be normal
- AHO (+)

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INTRODUCTION TO ADRENAL

Disorders of Adrenal 00:00:12

Adrenal Gland

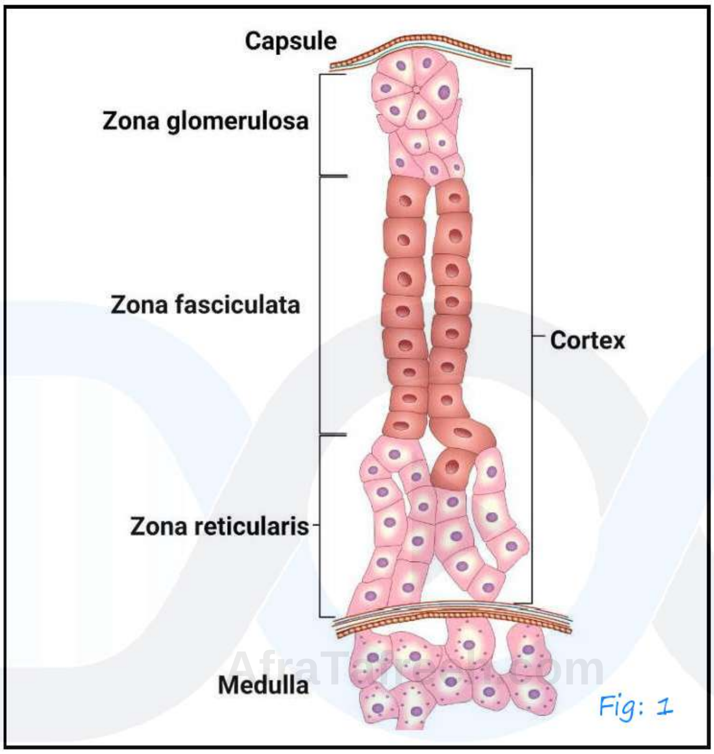

Fig: 1

- Adrenal gland has complex and medulla
- Cortex is further divided into
  - Zona glomerulosa → mineralocorticoids
  - Zona fasciculata → Glucocorticoids
  - Zona reticularis → adrenal androgens
- Classical example of mineralocorticoid – aldosterone

  Glucocorticoid – Cortisol

  Adrenal androgen – DHEA

  Dehydroepiandrosterone

  Androstenedione

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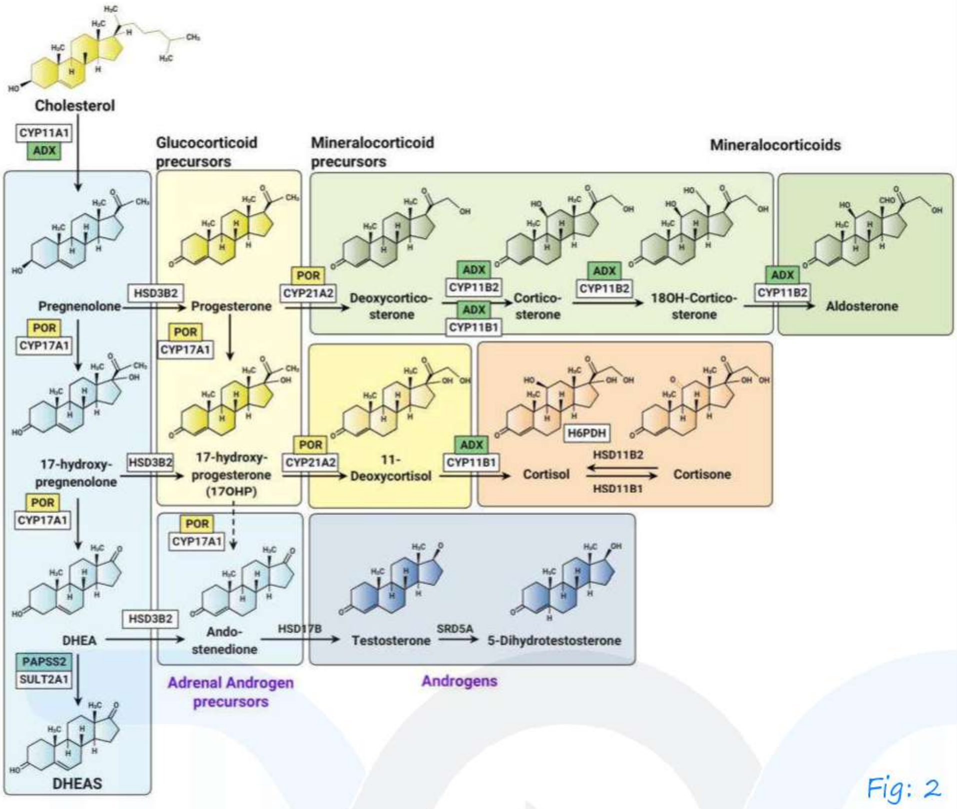

Fig: 2

- Corticosteroids, Adrenal androgens] are under the regulatory control of the hypothalamus & Pituitary
- Mineralocorticoids are basically controlled by RAAS (Renin Angiotensin Aldosterone System)

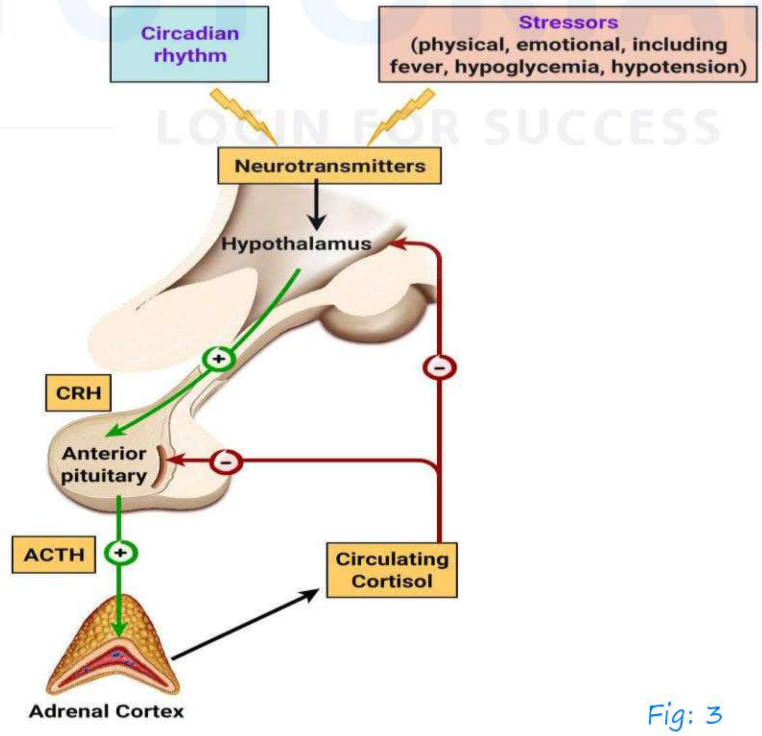

Fig: 3

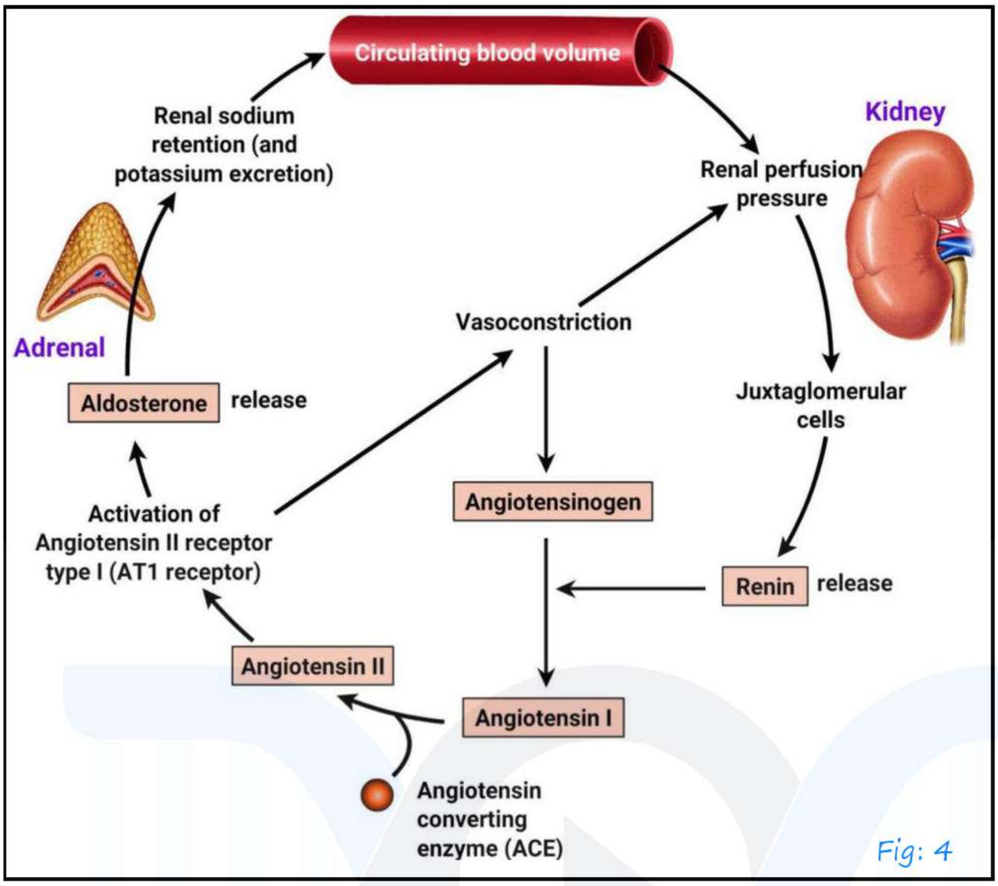

Fig: 4

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CUSHINGS SYNDROME

Cushing syndrome 00:00:16

Fig: 1

- Term cushing's was coined by Harvey cushing

Fig: 2

- Condition of
  - Chronic glucocorticoid excess (or)
  - Chronic hypercortisolism

- Classification

Endogenous

- ACTH dependent (90%)
- ACTH independent (10%)

- Most common cause of cushing syndrome – Iatrogenic

Causes of Cushing's Syndrome	Female: Male Ratio	%
ACTH dependent cushing's		90
Cushing's disease (=ACTH-producing pituitary adenoma)	4:1	75
Ectopic ACTH syndrome (due to ACTH secretion by bronchial or pancreatic carcinoid tumors, small-cell lung cancer, medullary thyroid carcinoma, pheochromocytoma and others)	1:1	15
ACTH Independent cushing's	4:1	10
Adrenocortical adenoma		5-10
Adrenocortical carcinoma		1
Rare cause: macronodular adrenal hyperplasia; primary pigmented nodular adrenal disease (micro and/or macronodular); McCune-Albright syndrome		<1

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- Cushing's disease – Cause is d/t pituitary.

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Clinical Features

- Increases cortisol – Glucocorticoid action
  - Mineralocorticoid action

↓

Affects metabolism of

- Carbohydrates → Increases gluconeogenesis
- Fats → Lipolysis, redistribution of body fat
- Proteins → protein catabolism

Body compartment/system	Signs and symptoms
Body fat	Weight gain, central obesity, rounded face, fat pad on back of neck ("buffalo hump")
Skin	Facial plethora, thin and brittle skin, easy bruising, broad and purple stretch marks, acne, hirsutism.
Bone	Osteopenia, osteoporosis (vertebral fractures), decreased linear growth in children.
Muscle	Weakness, proximal myopathy (prominent atrophy of gluteal and upper leg muscles with difficulty climbing stairs or getting up from a chair)

Cardiovascular system	Hypertension, hypokalemia, edema, atherosclerosis
Metabolism	Glucose intolerance/diabetes, dyslipidemia
Reproductive system	Decreased libido, in women amenorrhea (due to cortisol-mediated inhibition of gonadotropin release)
Central nervous system	Irritability, emotional lability, depression, sometimes cognitive defects; in severe cases, paranoid psychosis
Blood and immune system	Increased susceptibility to infections, increased white blood cell count, eosinopenia, hypercoagulation with increased risk of deep vein thrombosis and pulmonary embolism

Fig: 3

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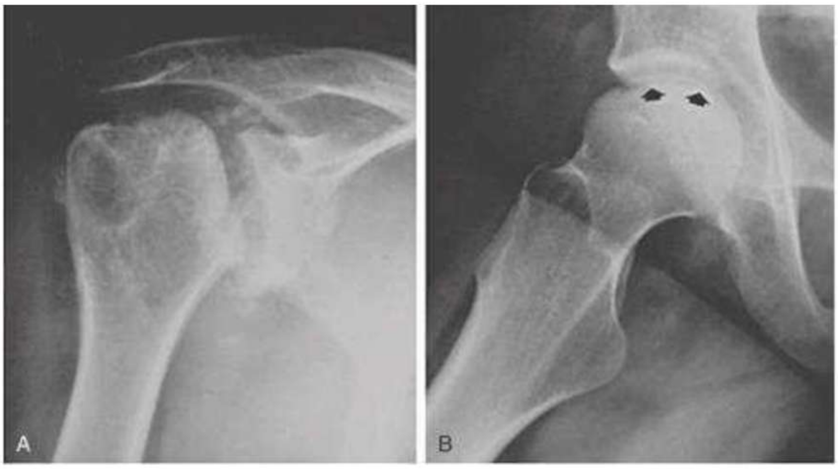
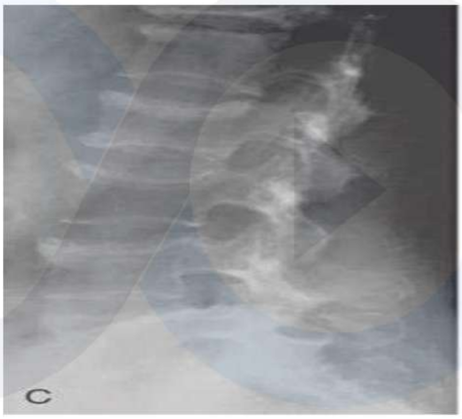


Aseptic necrosis of bone Fig: 4



Diffuse osteopenia Fig: 5

- In general, females > males
- In prepubertal age group – most common in males
- In ectopic ACTH males>females

Investigation of patient with clinically suspected cushings

1. Is this a cushing syndrome?
2. What is the cause?

- Increases cortisol

  90% cortisol is in bound form

  ↓

  cortisol binding globulin (CBG)

  ↓

  Affected when – Patient is on OCP's
  - Infection
  - Antiepileptics
  - Pregnancy
  - Post-partum

- Normally, cortisol secretion has circadian rhythm

  ↓

  Lowest levels – midnight

  Highest levels – early morning

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Clinical suspicion of cushing's

(Central adiposity, proximal myopathy, striae, amenorrhea, hirsutism, impaired glucose tolerance, diastolic hypertension, and osteoporosis)

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Screening/confirmation of diagnosis

- 24-h urinary free cortisol excretion increased above normal (3x)
- Dexamethasone overnight test (plasma cortisol > 50 nmol/L at 8-9 am after 1mg dexamethasone at 11pm)
- Midnight plasma cortisol >130 nmol/L

  (or midnight salivary cortisol > 5 nmol/L)

  If further confirmation needed/desired:
- Low dose DEX test (plasma cortisol > 50 nmol/L after 0.5 mg

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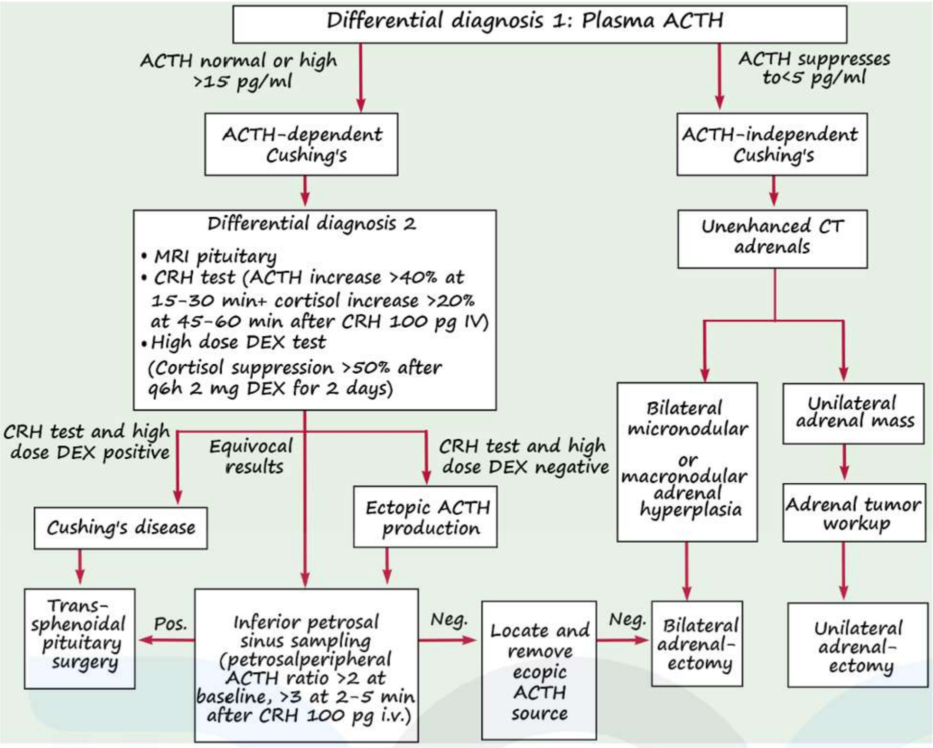

- MRI pituitary – Adenoma

  ↓

  Endoscopic Trans-sphenoidal resection
- Inferior petrosal sinus – venous sinus draining the pituitary region

  - Always rule out Iatrogenic causes

  ↓

  Patient on steroids
- Recurrence of pituitary tumor following surgery

  ↓

  Repeat surgery

  Radiotherapy
- Medical therapy post-surgery

  ↓

  - Metyrapone
  - Ketoconazole
  - Pasireotide
  - Mitotane – Adenocorticol cancer

HYPERALDOSTERONISM

- Mineralocorticoid excess

Primary hyperaldosteronism 00:00:42

- Increased production of aldosterone from zona glomerulosa
- 2 reasons
- Bilateral adrenal hyperplasia (60%)
- Adrenal adenoma → CONN's syndrome (30%)

Clinical manifestations

- ↑ Aldosterone → N^+ + H2O retention → Diastolic HTN, Hypokalemia, Alkalosis, No edema because of ANP

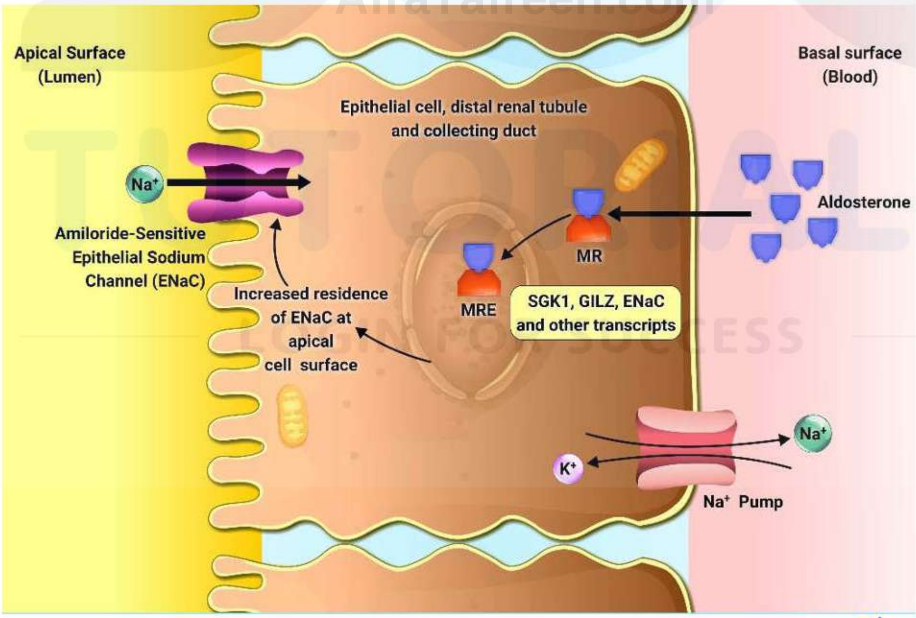

Fig: 1

Clinical suspicion of mineral corticoid excess

- Patients with hypertension and
- Severe hypotension (>3 BP drugs drug – resistant) or
- Hypokalemia (spontaneous or diuretic induced) or

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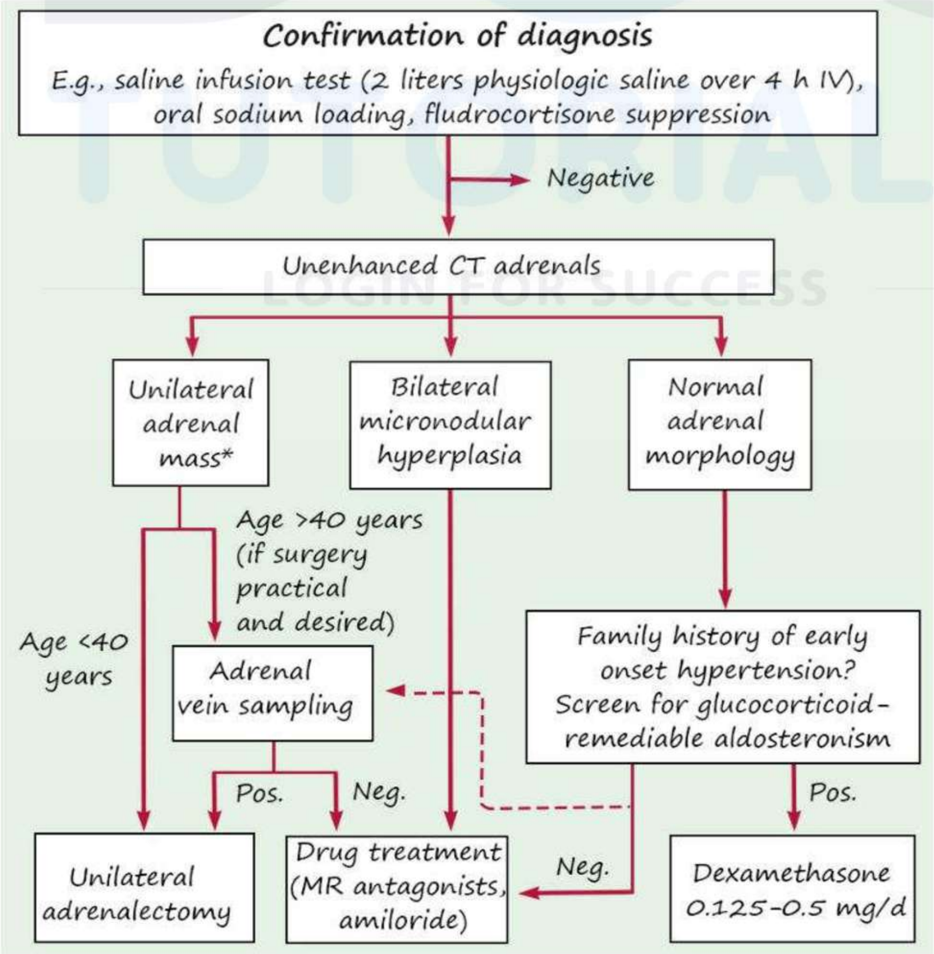
- Adrenal mass or
- Family history of early onset hypertension or cerebrovascular events at <40yrs of age

Screening tests

- Aldosterone – Renin ration → Increased
- Morning blood sample in seated ambulant patient
- Plasma aldosterone concertation (PAC)
- Plasma renin activity (PRA) or PRC
- ↑PAC (≥ 10ng/dl)
- ↓PRA (<1ng/ml/hr) or
- ↓ PRC (<Lower limit of normal for the assay)
- Investigate for primary aldosteronism
- Spironolactone can interfere with PAC/PRA

  ↓

  Stop for 4weeks before doing test



Drugs given

- Spironolactone
- Eplerenone
- Adrenal venous sampling AVS
- Invasive procedure

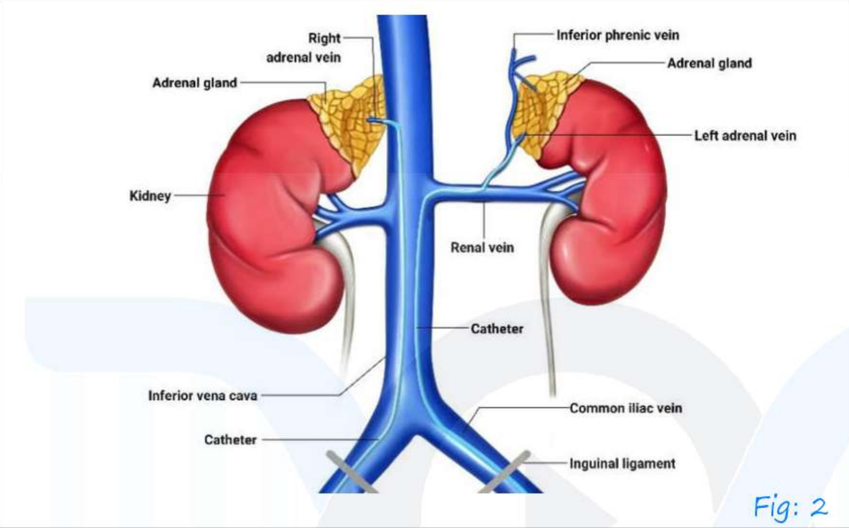


Fig: 2

- Catheter is introduced into the femoral veins

One targeting (R) adrenal vein | One targeting (L) adrenal vein

- Estimate aldosterone levels in these venous samples
- If lateralization (+) (Aldosterone levels high on (R) side)

↓

Indicates which is problematic

Glucocorticoid remediable aldosteronism

- Normally, aldosterone production is under control of RAAS
- There is a cross over mutation leading to chimeric state in which aldosterone would be under control of ACTH

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- If steroids (dexa) are given, by negative feedback, it will inhibit ACTH and subsequent aldosterone production also decreased

Mineralocorticoid excess syndrome

Low renin (AngII independent)

- High Aldosterone → Primary aldosteronism
  - Unilateral
  - Bilateral
  - Familial genetic
- Low Aldosterone → Pseudo Primary aldosteronism
  - Acquired
  - Hypercortisolism
  - Licorice toxicity (11beta HSD2 inhibition)
  - Genetic
  - Syndrome of apparent mineralocorticoid excess (loss of function mutation in 11beta HSD2)
  - Activating mutation of the mineralocorticoid receptor
  - Liddle syndrome (gain of function of ENaC)
  - Congenital adrenal hyperplasia (11beta OH deficiency 17alpha OH deficiency)

High renin (AngII dependent) → Secondary aldosteronism

- Hypertensive
- Renal artery stenosis
- Aortic coarctation
- Rwninoma (Extremely rare)
- Normotensive
- Gittleman's syndrome
- Bartter's syndrome

Pseudo Primary Aldosteronism

↓

1. SAME: Syndrome of apparent mineralocorticoid excess
2. Liddle syndrome

Same

- Defect of enzyme 11beta hydroxysteroid dehydrogenase

↓

Cortisol ⟶ Cortisone

↓

↑ Cortisol

↓

Mineralocorticoids are responsible for symptoms

↓

Hypertension

Hypokalemia

Alkalosis

- Treatment:
  - Spironolactone
  - Eplerenone
  - Dexamethasone → (↓) ACTH

Liddle syndrome

- AD
- Activating mutation involving ENAC

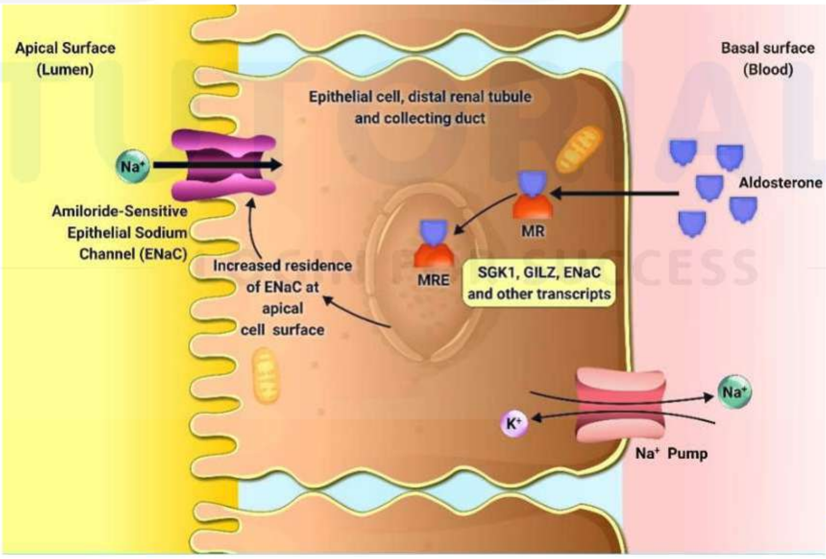

Fig: 3

- Clinical features
  - Hypertension
  - Hypokalemia
  - Alkalosis
- Treatment:
  - Amiloride

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ADRENAL INSUFFICIENCY

Adrenal Insufficiency 00:00:05

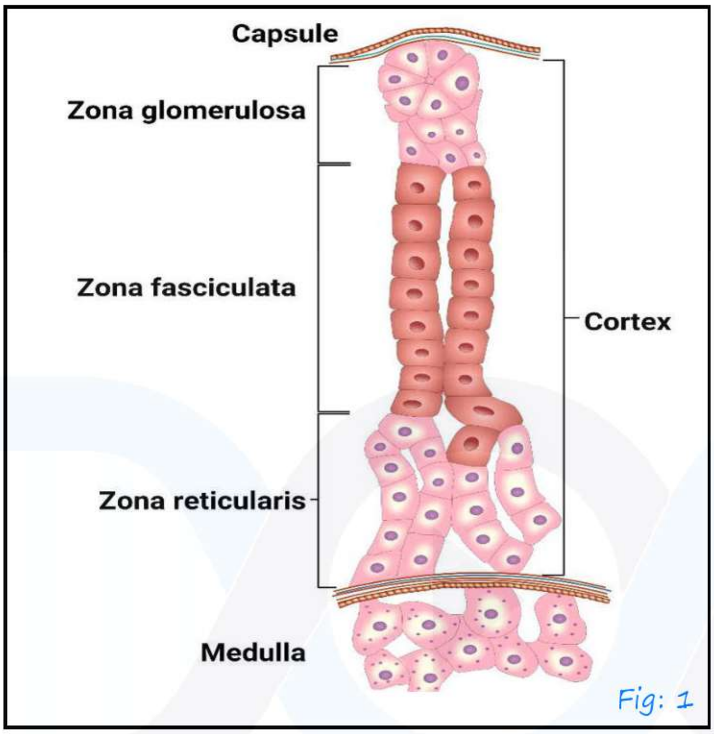

Fig: 1

- Zona glomerulosa → aldosterone
- Zona fasciculata → cortisol
- Zona reticularis → DHEA (Dehydroepiandrosterone Androstenedione)

Adrenal insufficiency

1° adrenal insufficiency	2° adrenal insufficiency
↓	↓
Problem is in adrenals	Problem hypothalamo pituitary axis
↓	
Addison's disease	

1° adrenal insufficiency 00:02:50

- Hormone production from all 3 layers affected
  - Decrease aldosterone
  - Decrease cortisol
  - Decrease DHEA, androstenedione
- Increase ACTH

2° adrenal insufficiency 00:04:14

- Often a result of primary tumor
  - Normal aldosterone levels
  - Decrease cortisol
  - Decrease DHEA
  - Decrease androstenedione
- Decrease ACTH

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Iatrogenic adrenal insufficiency

ITP patient taking steroids

↓

When patient is on long term steroids

↓

This can suppress pituitary & hypothalamus

- When steroids are stopped suddenly, pituitary is in suppression state and results in adrenal insufficiency

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Etiology of 1° adrenal insufficiency 00:08:41

- Most common causes – Autoimmune (western) → Indian-TB
- Autoimmune conditions
  - Isolated autoimmune adrenalitis
  - APS-1 (Autoimmune polyglandular syndrome)
  - APS-2
- Other infections
  - HIV
  - Histoplasmosis
- Genetic conditions

Congenital adrenal hyperplasia

Adrenoleukodystrophy

↓

Peroxisomal transport protein defect

- Adrenal metastasis

Clinical features 00:13:20

- 1° darnel insufficiency

Signs and Symptoms Caused by Glucocorticoid Deficiency

- Fatigue, lack of energy
- Weight loss, anorexia
- Myalgia, joint pain
- Fever
- Normochromic anemia, lymphocytosis, eosinophilia

- Slightly increased TSH (due to loss of feedback inhibition of TSH release)
- Hypoglycemia (more frequent in children)
- Low blood pressure, postural hypotension
- Hyponatremia (due to loss of feedback inhibition of AVP release)

Signs and Symptoms Caused by Mineralocorticoid Deficiency (Primary Adrenal Insufficiency Only)

- Abdominal pain, nausea, vomiting
- Dizziness, postural hypotension
- Site craving
- Low blood pressure, postural hypotension
- Increased serum creatinine (due to volume depletion)
- Hyponatremia
- Hyperkalemia

Signs and Symptoms Caused by Adrenal Androgen Deficiency

- Lack of energy
- Dry and itchy skin (in women)
- Loss of libido (in women)
- Loss of axillary and pubic hair (in women)

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Other Signs and Symptoms

- Hyperpigmentation (primary adrenal insufficiency only) (due to excess of proopiomelanocortin [POMC]-derived peptides)
- Alabaster-colored pale skin (secondary adrenal insufficiency only) (due to deficiency of POMC-derived peptides)
  - In 1° adrenal insufficient – hypovolemic hyponatremia
  - 2° adrenal insufficient – euvolemic hyponatremia

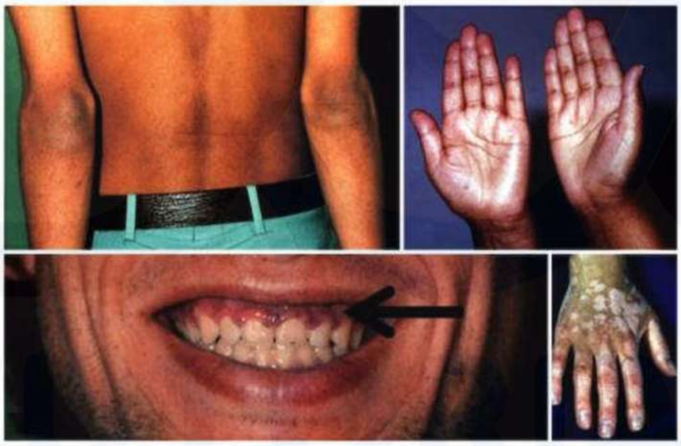
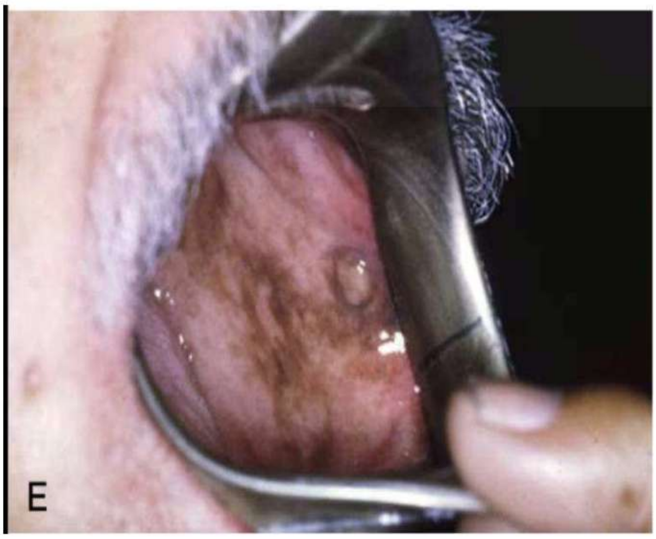


Fig: 2

- Vitiligo – signature of autoimmunity



Oral mucosal hyperpigmentation Fig: 3

Adrenal crisis/Addisonian crisis 00:25:10

- Endocrine emergency

Clinical and laboratory features of an adrenal crisis

- Dehydration, hypotension, or shock out of proportion to severity of current illness
- Nausea and vomiting with a history of weight loss and anorexia
- Abdominal pain, so-called acute abdomen
- Unexplained hypoglycemia
- Unexplained fever
- Hyponatremia, hyperkalemia, azotemia, hypercalcemia, or eosinophilia
- Hyperpigmentation or vitiligo
- Other autoimmune endocrine deficiencies, such as hypothyroidism (or) gonadal failure

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Features

- Hypovolemic shock
- Acute abdomen → due to hypercalcemia

Investigations 00:27:53

- High index of clinical suspicion
- No rule for random cortisol

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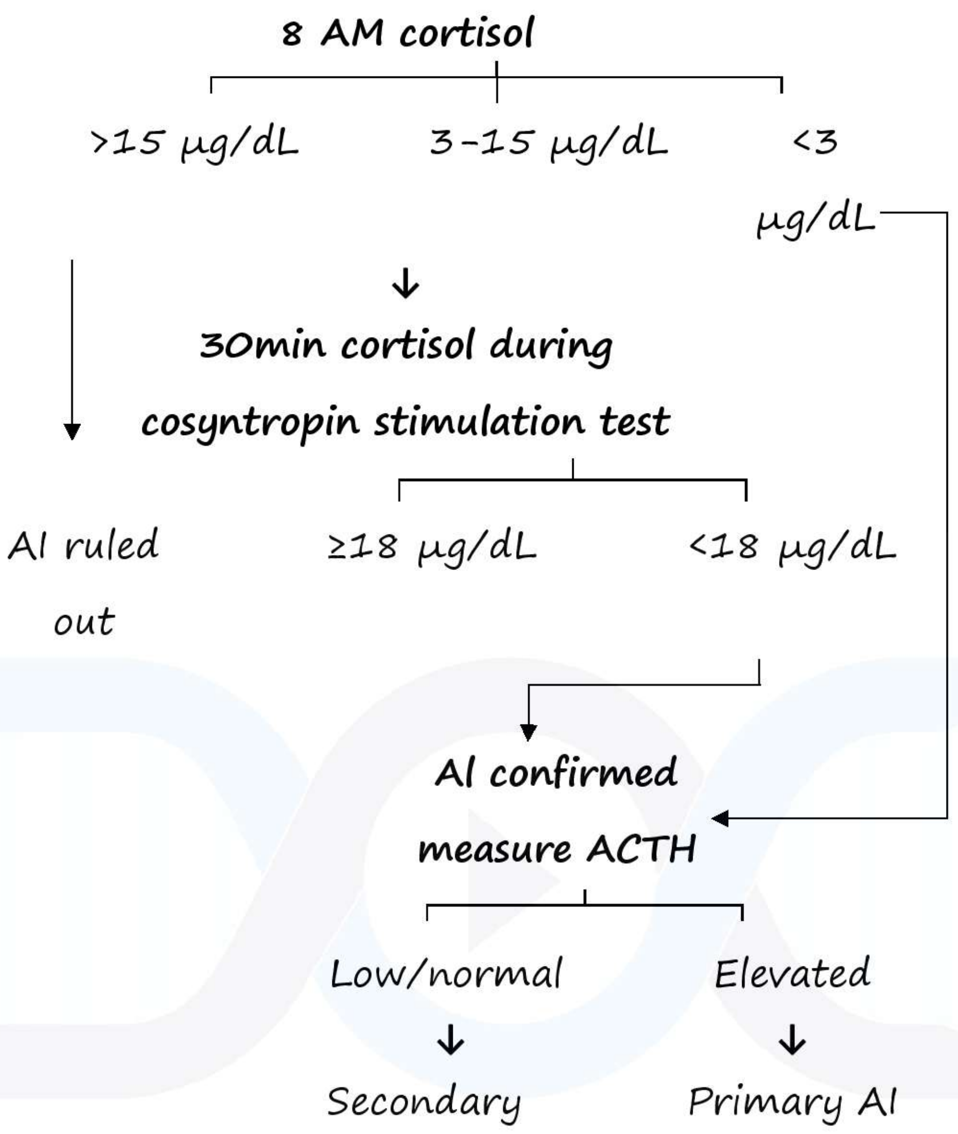

ACTH stimulation test

- 250 μg of ACTH given iv/im → cortisol <18 μg/dL
  ↓
  Adrenal insufficiency

- Co-syntropin test
- Synacthen test

Management 00:33:00

i. Chronic adrenal insufficiency

ii. Addisonian crisis

Chronic adrenal insufficiency

- Replace glucocorticoids – Hydrocortisone
  (15-25mg/day in 2-3 doses)
  ↓
  50% dose in morning
- Mineralocorticoids – Fludrocortisone (100-150μg/day)
- Adrenal androgens – only when there is non response with glucocorticoids and mineralocorticoids – DHEA

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Addisonian crisis

- Endocrine emergency
  - i. Fluid replacement – Infusion of normal saline
    - Hypoglycemia ⊕ → Dextrose infusion
  - ii. Glucocorticoids
    - Hydrocortisone – parenterally (100mg – 8th hourly)
  - iii. Mineralocorticoids
    - Fludrocortisone – same cases when hydrocortisone is being tapered

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PHEOCHROMOCYTOMA

Disorders of adrenal medulla 00:00:16

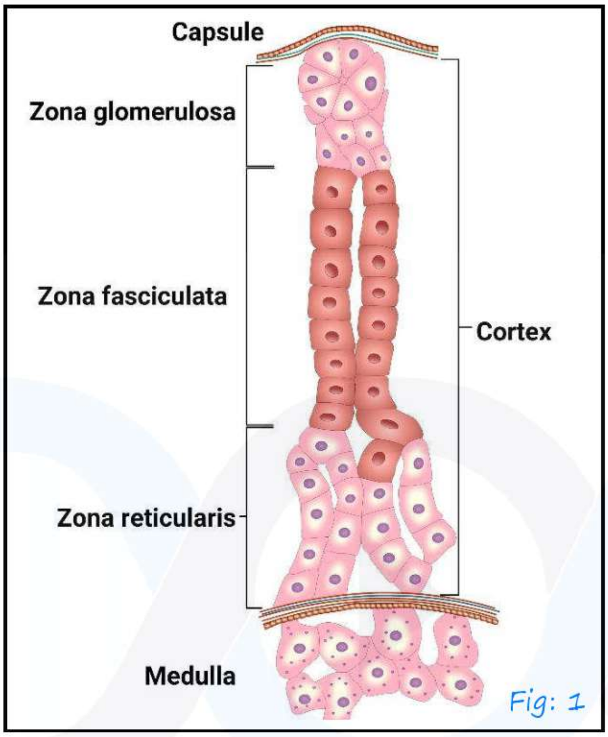

Fig: 1

- Adrenal consists of some chromaffin cells
- The cells in adrenal medulla are responsible for release of catecholamines
  - Adrenaline (epinephrine) → Highest amount
  - Noradrenaline (not epinephrine)
  - Dopamine

Biosynthesis of catecholamines

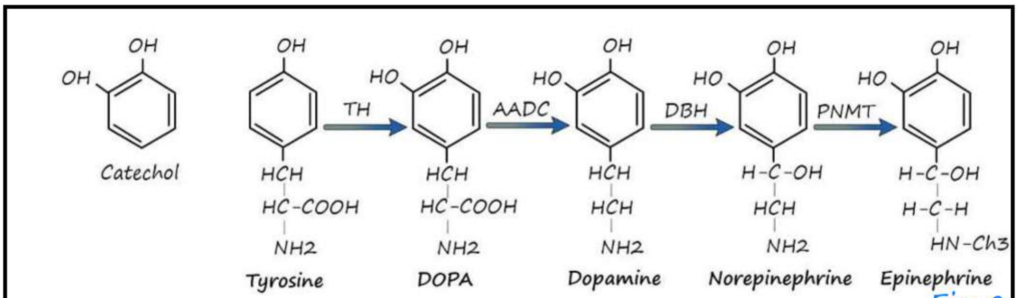

Fig: 2

- Dopamine —**Dopamine beta hydroxylase**→ Norepinephrine
- Norepinephrine —**Phenyl ethanolamine N-methyl transferase**→ Epinephrine

↓

Induced by cortisol

Pheochromocytomas 00:04:04

- Catecholamine producing tumors
- Can be of adrenal (75-80%) origin (or) extra adrenal (20-25) origin
  - Sympathetic & parasympathetic ganglia
  - Paraganglioma

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Rule of 10

- 10% extra adrenal
- 10% bilateral
- 10% malignant

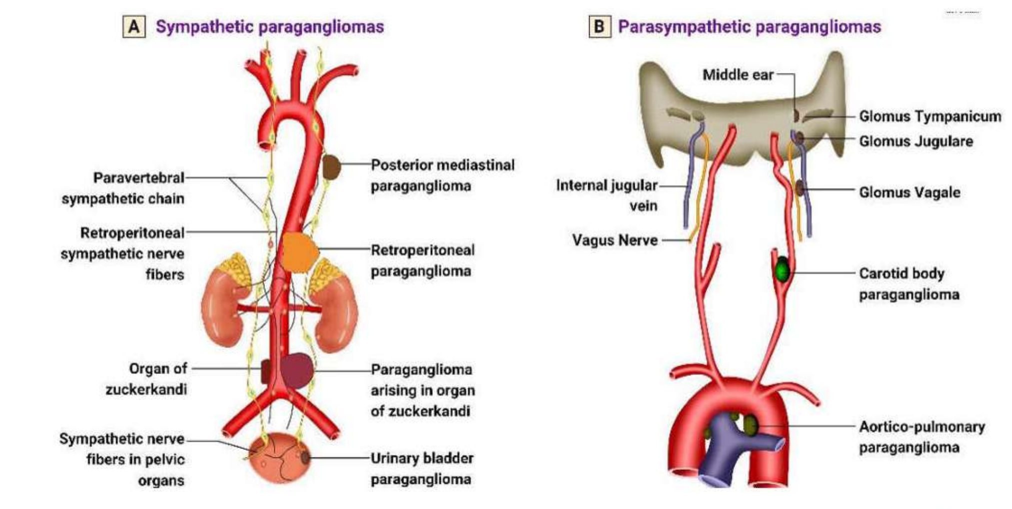

Fig: 3

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Etiology

i. 70% sporadic → 40 years

ii. 30% familial

- 20's & 30's

- Associated with
  - MEN 2A
  - MEN 2B
  - Von hippel lindau syndrome
  - NF type I
- Bilateral

Clinical features

- Catecholamine surge occurs episodically

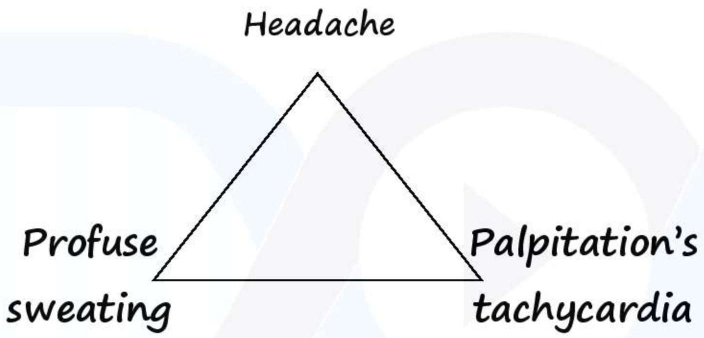
Clinical features associated with pheochromocytoma listed by frequency of occurrence 00:10:32

---

1. Headaches
2. Profuse sweating
3. Palpitations and tachycardia
4. Hypertension, sustained (or) paroxysmal
5. Anxiety and panic attacks
6. Pallor
7. Nausea
8. Abdominal pain
9. Weakness
10. Weight loss
11. Paradoxical response to antihypertension drugs

12. Polyuria and polydipsia
13. Constipation
14. Orthostatic hypotension
15. Dilated cardiomyopathy
16. Elevated blood sugar
17. Hypercalcemia

- Characteristic triad



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Investigation

- Estimation of fractionated products of catecholamine
- Most abundant catecholamine secreted by
  - i. Adrenal → Adrenaline
  - ii. Extra adrenal → Nor adrenaline

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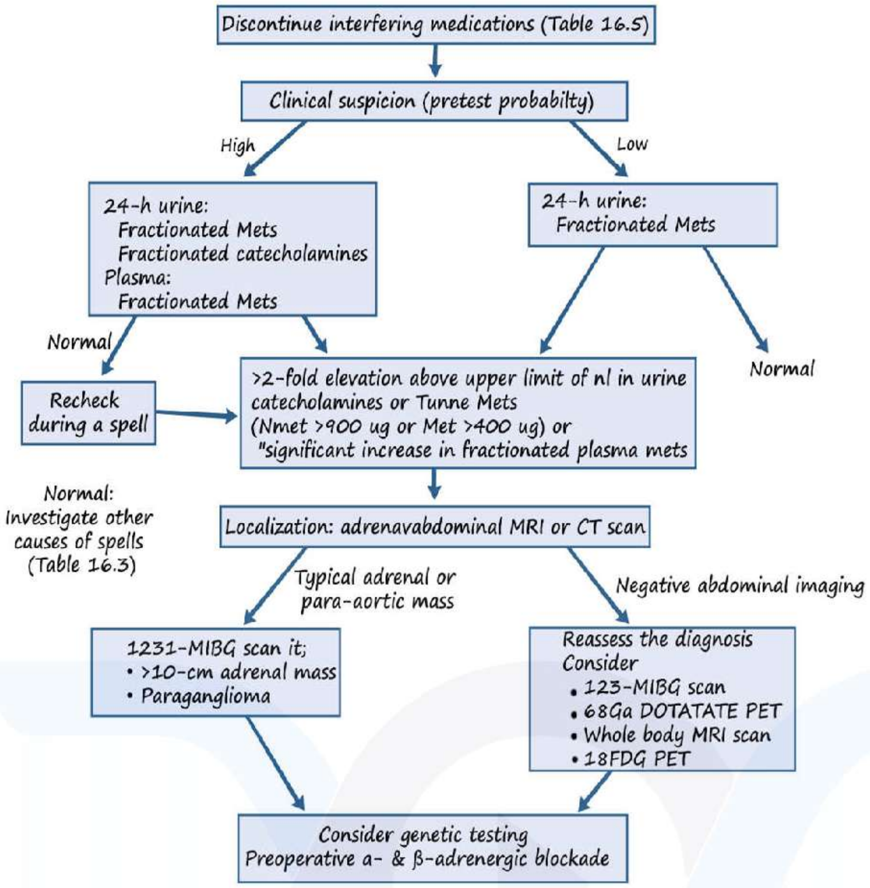

Medications that may increase measured levels of fractionated catecholamines and metanephrines

- Tricyclic antidepressants (including cyclobenzaprine)
- Levodopa
- Drugs containing adrenergic receptor agonists (e.g., decongestants)
- Amphetamines
- Buspirone and antipsychotic agents
- Prochlorperazine
- Reserpine
- With-drawl from clonidine and other drugs (e.g., illicit drugs)
- Illicit drugs (e.g., cocaine, heroin)
- Ethanol

- IOC for adrenal pheochromocytoma – CEMRI
- IOC for extra adrenal pheochromocytoma – Dotate PET scan

Planning for surgery

- α blockade f/b β blockade →propranolol
  - Phenoxybenzamine (DOC)
  - Phentolamine
  - Prazosin
  - Doxazosin

Treatment of HTN crisis

- Phentolamine
- Sodium nitroprusside
- Nicardipine

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Intravenously administered drugs used to treat pheochromocytoma

Agent	Dosage range
For hypertension	
Phentolamine	Administer a 1-mg IV test done, then 2-mg to 5-mg IV boluses as needed (or) continuous infusion
Nitroprusside	IV infusion rates of 2 μg/kg of body wight per minute are suggested as safe. Rates >4 μg/kg per minute may lead to cyanide toxicity within 3 hours. Doses >10 μg/kg per minute are rarely required, and the maximal dose should not exceed 800 μg/min
Nicardipine	Initiate therapy at 5mg/hr; the IV infusion rate may be increased by 2.5 mg/hr q15 min up to a maximum of 15mg/hr

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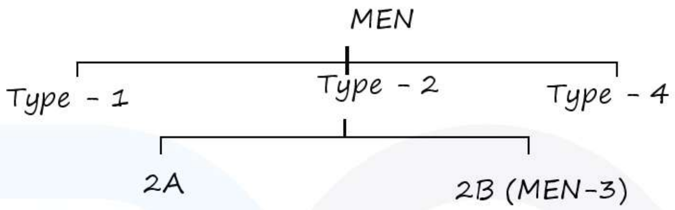
MEN & MEONS

Multiple endocrine neoplasia (MEN) 00:00:05

- ≥ 2 endocrine tumors
- Familial
- Autosomal dominant



Werner syndrome
↓
Adult progeria premature ageing

MEN – 1 00:04:00

- Wermer syndrome

Multiple Endocrine Neoplasia (MEN) Syndromes		
MEN 1 (11q13)	Parathyroid adenoma (90%) Enteropancreatic tumor (30-70%) - Gastrinoma (>50%) - Insulinoma (10-30%) - Nonfunctioning and PPoma (20-55%)	MEN 1 83/84, 4-bp del (≈4%) 119, 3-bp del (≈3%) 209-211, 4-bp del (≈8%)

	- Glucagonoma (<3%) - VIPoma (<1%) Pituitary adenoma (15 – 50%) - Prolactinoma (60%) - Somatotrophinoma (25%) - Cortiocotropinoma (<5%) - Non functioning (<5%) Associated tumors - Adrenal cortical tumor - Pheochromocytoma (<1%) - Bronchopulmonary NET (2%) - Thymic NET (2%) - Gastric NET (10%)	418, 3-bp del (=4%) 514-516, del or ins (=7%) Intron 4 ss (=10%)

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- MEN I gene- MENIN
- Chr 11q

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- 3P's- parathyroid, pancreas, pituitary
- Parathyroid gland would be affected first Primary Hyperparathyroidism → Hypercalcemia
- Most common in MEN - I Parathyroid adenoma
- Most common Entero pancreatic tumor – Gastrinoma
- Most common Pituitary affection - Prolactinoma

Multiple endocrine neoplasia (MEN) syndromes		
Type (Chromosomal location)	Tumors (Estimated penetrance)	Gene and most frequently mutated codons
MEN 1 (11q13)	Parathyroid adenoma (90%) Enteropancreatic tumor (30-70%) • Gastrinoma (>50%) • Insulinoma (10-30%) • Nonfunctioning and PPoma • (20-55%) • Glucagonoma (<3%) • VIPoma (<1%) • Pituitary adenoma (15-50%) • Prolactinoma (60%) • Somatotrophin Oma (25%) • Corticotrophin (<5%) • Nonfunctioning (<5%) • Associated tumors • Adrenal cortical tumor • (20-70%) • Pheochromocytoma (<1%) • Bronchopulmonary NET (2%) • Thymic NET (2%) • Gastric NFT (10%) • Lipomas (:33%) • Angiofibroma (85%) • Collagenomas(70%) • Meningioma (8%)	Men1 83/84, 4-bp del (≈4%) 119, 3-bp del (≈3%) 209-211, 4-bp del (≈8%) 418, 3-bp del (≈4%) 514-516, del or ins (≈7%) Intron 4ss (≈10%)

MEN -2 00:13:16

- Sipple syndrome

MEN 2 (10 cen-10q11.2) MEN 2A	MTC (90%) Pheochromocytoma (>50%) Parathyroid adenoma (10-25%) MTC (100%)	RET 634, e.g., Cys → Arg (~85%)
MTC only	MTC (100%)	RET 618, missense (>50%)
MEN 2B (also known as MEN 3)	MTC (>90%) Pheochromocytoma (>50%) Associated abnormalities (40-50%) - Mucosal neuromas - Marfanoid habitus - Medullated corneal nerve fibers - Megacolon	RET 618, missense (>50%) RET 918, Met → Thr (>95%)

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Fig: 1

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- Hyperpigmented violaceous scaly plaques
- Cutaneous Lichen Amyloidosis
- Feature of MEN 2A

Fig: 2

- Mucosal Neuromas Slit lamp - medullated corneal fibers → MEN 2B

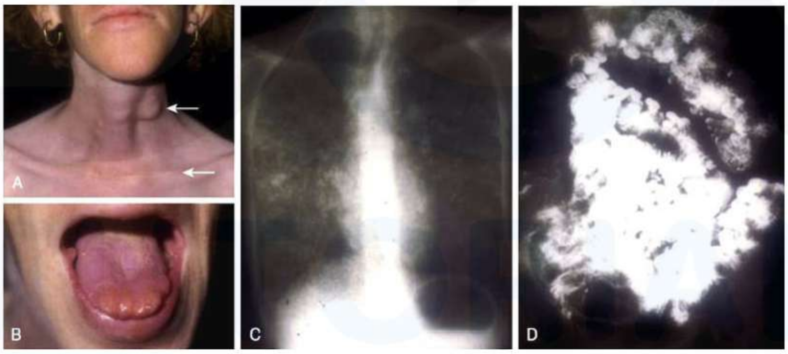

Fig: 3

MEN-4 00:22:10

- Parathyroid adenoma
- Pituitary adenoma
- Reproduction organ tumors (e.g., testicular cancer, neuroendocrine cervical carcinoma)
- ? Adrenal + renal tumors
- CDKN1B: No common mutations identified to date
- Chromosome 12 p

Multiple Endocrine and Other Organ Neoplasia Syndromes (MEONs)		
Disease	**Gene Product**	**Chromosomal Location**
Hyperparathyroidism – jaw tumor (HPT-JT)	Parafibromin	1q31.2
Carney Complex CNC1 CNC2	 PPKAR1A ?	 17q24.2 2p16
Von Hippel-Lindau disease (VHL)	pVHL (elongin)	3p25
Neurofibromatosis type 1 (NF1)	Neurofibromin	17q11.2
Cowden's syndrome (CWS) CWS 1 CWS 2 CWS 3 CWS 4 CWS 5 CWS 6 CWS 7	 PTEN SDHB SDHD KLLN PIK3CA AKT1 SEC23B	 10q23.31 1p36.13 11q23.1 10q23.31 3q26.32 14q32.33 20p11.23
Mc Cune-Albright syndrome (MAS)	Gsα	20q13.32

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- Multiple endocrines and other organ neoplasia
- 6 MEON'S
- McCune- Albright syndrome (MAS)

↓

Post zygotic somatic cell mutation (Mosaicism)

Carney's Complex 00:29:30

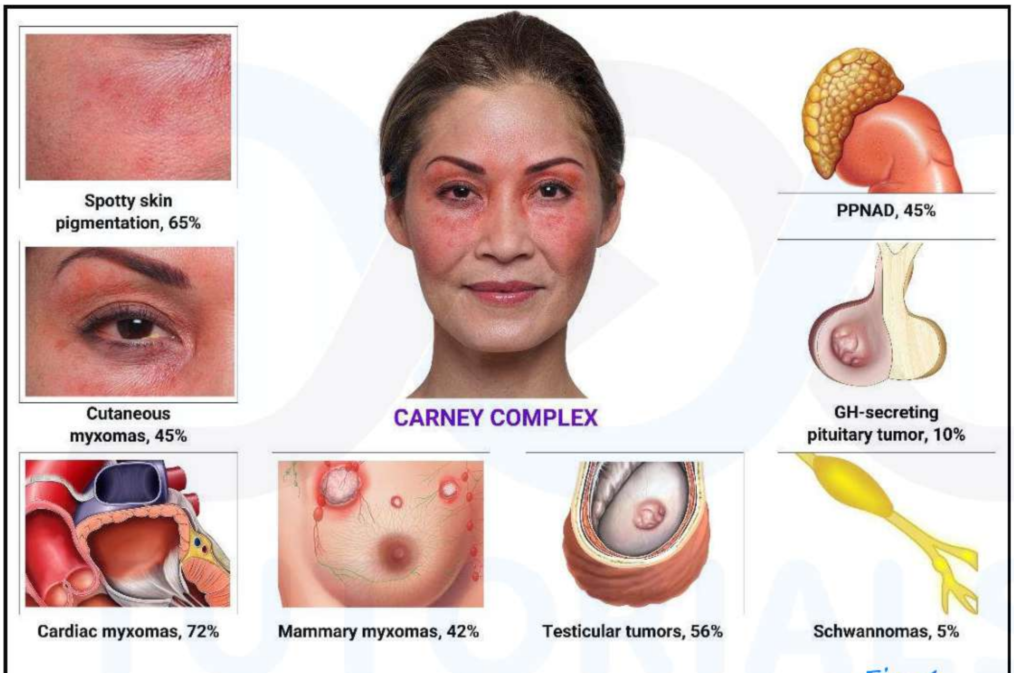

Fig: 4

- Hyperpigmentation
- Cutaneous myxomas
- Cardiac myxomas
- Mammary myxomas
- Testicular tumors
- Schwannomas
- GH Secreting pituitary tumor
- PPNAD → Primary pigmented Nodular Adrenal Hyperplasia

INTRODUCTION AND CLASSIFICATION OF DM

Diabetes mellitus 00:00:18

Fig: 1

Classification of Diabetes 00:01:45

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- Diabetes can be classified into the following general categories

  1. Type 1 diabetes (due to autoimmune B-cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes of adulthood)
  2. Type 2 diabetes (due to a progressive loss of B-cell insulin secretion frequently on the background of insulin resistance)
  3. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young),

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diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)

4. Gestational diabetes mellitus (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)

- Type I DM → IDDM – Insulin dependent diabetes mellitus
- Auto immune destruction of pancreatic islets
- Both T cells and B cells would contribute insulitis
- Decreases in beta cell population

Susceptibility genes
IDDM 1-22

Environment triggers
virus Dietary factors
toxins

Induction of autoimmunity

T cell mediated attack on beta cells
↓
Beta cell destruction
Insulin dependence
Type 1 diabetes

Activation of beta cells
↓
Autoantibodies (Markers of autoimmunity)
GAD65
ICA
IA2
Zn T8
Others

- Anti-GAD antibody (Glutamic acid decarboxylase)
- Anti-ICA (islet cell antigen)
- Anti IA2
- Anti Zn T8 (Zinc transporter)
- In type I, since insulin release is decreased because of beta cells

  ↓

  C – Peptide levels low

Type II DM

- Non IDDM
- Result of insulin resistance
- Ominous octet

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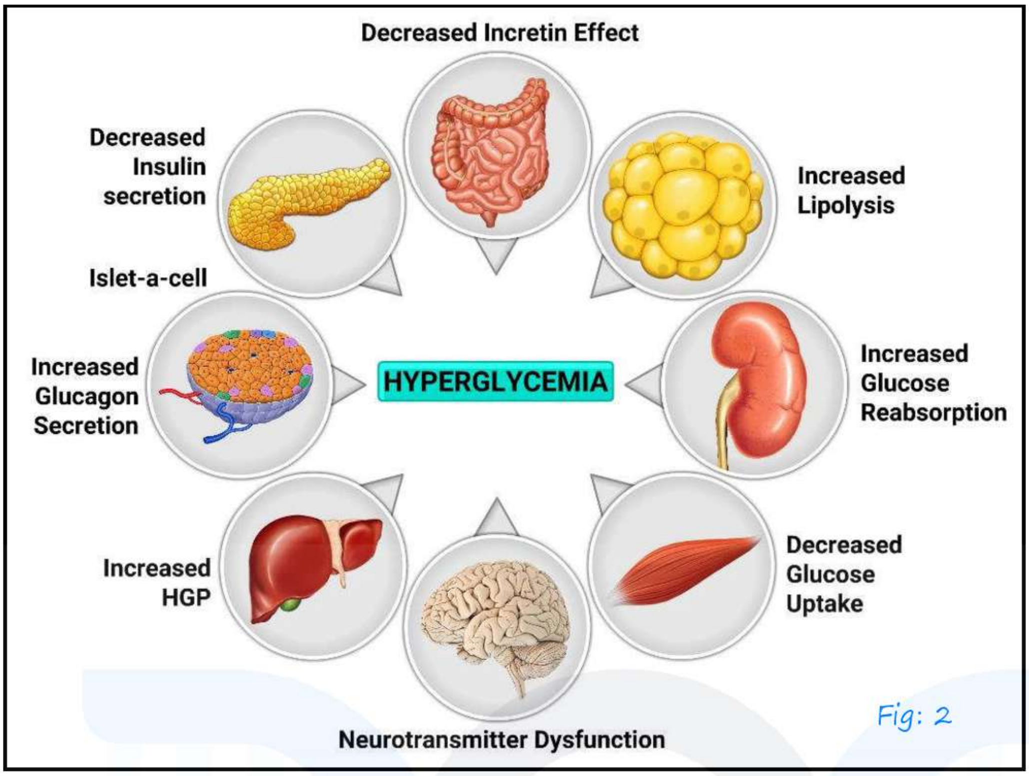
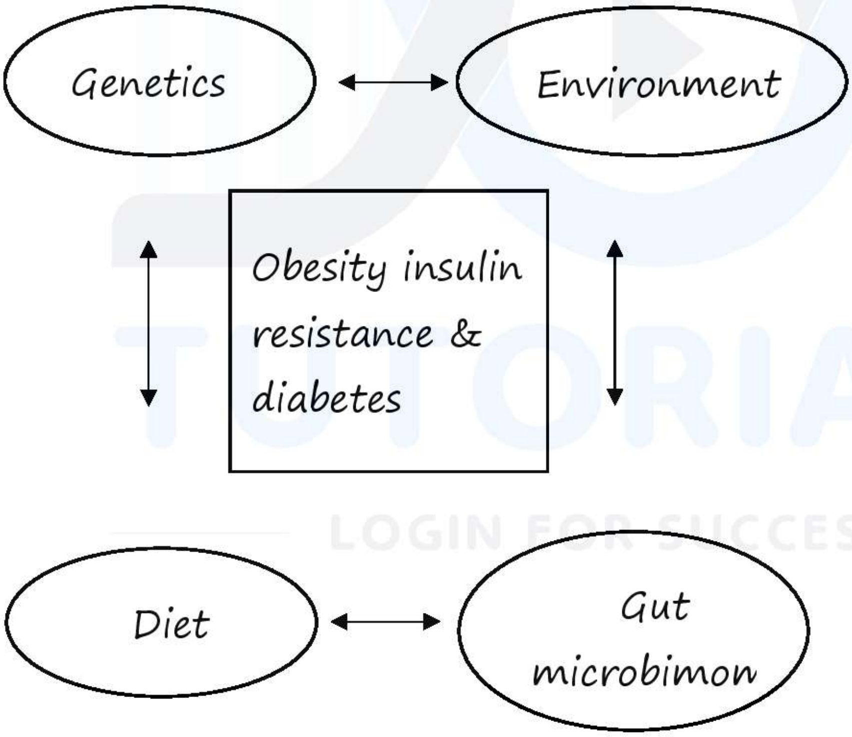


Fig: 2



S/No	Features	Type 1	Type 2
1.	Frequency	10% 20%	80% 90%
2.	Age of onset	Early <35y	Late >40y

3.	Type of onset	Abrupt and severe	Gradual and insidious
4.	Weight	Normal	Obese or nonobese
5.	HLA	Linked to HLA, DR3, HLA DR4, HLA DQ	No HLA association
6.	Family history	<20%	Approximately 60%
7.	Genetic locus	Unknown	Chromosomes 6
8.	Diabetes in identical twins	50% concordance	80% concordance
9.	Pathogenesis	Autoimmune destruction of beta cells	Insulin resistance impaired insulin secretion
10.	Islets of cell antibodies	Decreased insulin	No
11.	Blood insulin level	Decreased insulin	Normal or increased insulin
12.	Islet – cell changes	Insulin cell depletion	No insulitis late fibrosis
13.	Amyloidosis	Infrequent	Common in chronic cases
14.	Clinical management	Insulin diet	Diet, exercise, oral drugs, insulin
15.	Acute complications	Ketoacidosis	Hyperosmolar coma

- Excessive thirst
- Polyuria
- Polydipsia
- Sometimes may present as DKA

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- Obese patients, acanthosis nigricans →Trigger's insulin resistance
- Lack of exercise

LADA

- If a person develops hyperglycemia in early 30's or late 40's

↓

OHA

↓

Insulin dependent

↓

Pt has autoantibodies

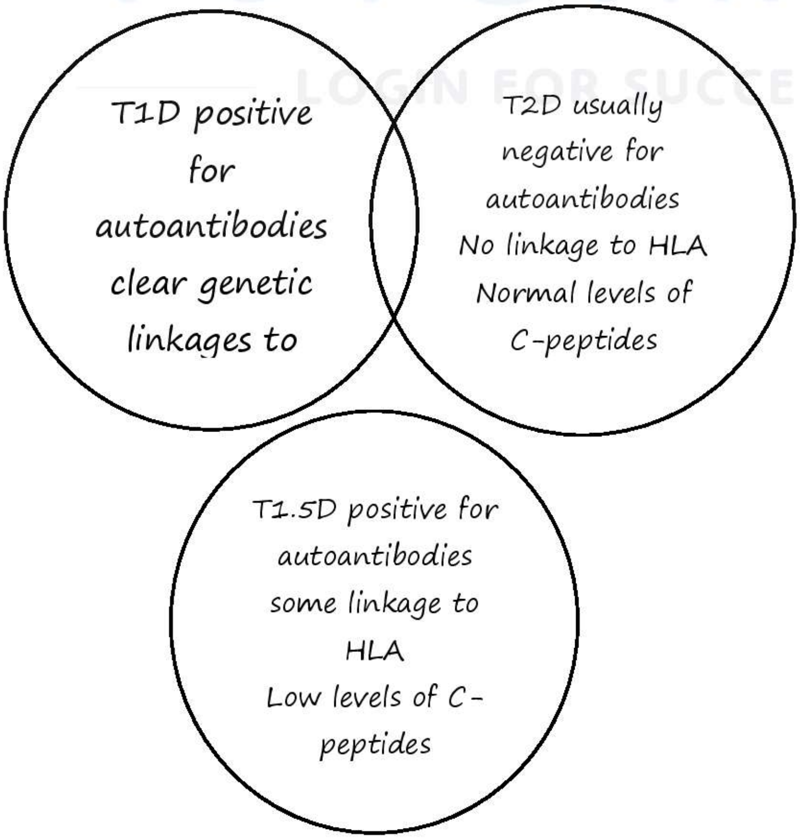
↓

CADA (latent autoimmune diabetes of adults)

↓

No features of insulin resistance

- Referred to as 1.5 diabetes



Features	Type 2 DM	LADA	Type 1Dm
Metabolic syndrome components	Frequently present	Usually, absent	Less frequent
Keto acidosis	Less common	Usually absent at diagnosis but could be present	Frequently
Cardiovascular complication	Increased	Same as in type 2 DM	Increased
Microvascular complications	Increased	Same as in type 2 DM	Increased
Pancreatic autoantibodies	Absent	Positive	Positive

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Ketosis prone diabetes (KPD)

- Type 2 DM
- Earlier presentation
- Presents with DKA
- Phenotype of metabolic syndrome
- Obese
- Acanthosis nigricans
- Initially requires insulin, later responds well to OHA

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MODY

- Maturity onset diabetes of young
- AD
- Monogenic

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- Age < 25yrs
- Strong family history

Clinical features	Type 1 diabetes mellitus	Type 2 diabetes mellitus	MODY
Age of diagnosis (Years)	Majority <25, but may occur at any age	Typically, >25 but incidence is increasing in adolescents paralleling increasing rates of obesity in children and adolescents	<25
Weight	Usually thin, but with obesity epidemic overweight and	>90% at least overweight	Similar to general population

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	obesity at diagnosis becoming more common		
Auto antibodies	Present	Absent	Absent
Insulin dependent	Yes	No	No
Insulin sensitivity	Normal when controlled	Decreased	Normal (May be decreased if obese)
Family history of diabetes	Infrequent (5 to 10%)	Frequent (75 to 90%)	Multigenerational i,e. >2 generations
Risk of diabetic ketoacidosis	High	Low	Low

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- Maturity onset diabetes of the young commonly identified gene mutations

Type	Genetic defect	Frequency	Beta cell defect
1	Hepatocyte nuclear factor – 4 alphas	<10%	Reduced insulin secretory response to glucose

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2	Glucokinase	15 to 31%	Defective glucokinase molecule (Glucose sensor) increased plasma level of glucose are necessary to elicit normal levels of insulin secretion
3	Hepatocyte nuclear factor – 1 alpha	52 to 65%	Abnormal insulin secretion low renal threshold for glucose
4	Insulin promoter factor 1	Rare	Reduced binding to the insulin gene promoter reduced activation of insulin gene in response to hyperglycemia
5	Hepatocyte nuclear factor – 1beta	Rare	
6	Neurogenic differentiation factor - 1	Rare	Pancreatic development

DOT TUTORIALS LOGIN FOR SUCCESS

Type	Clinical features	Risk of microvascular disease	Optimal treatment
1	Normal renal threshold for glucose	Yes	Sulfonylureas
2	Mild stable fasting hyperglycemia often diagnosed during routine screening not progressive	Generally, no	Diet
3	Low renal threshold for glucose + Glycosuria	Yes	Sulfonylureas
4	Rare pancreatic agenesis in homozygotes less severe mutation result in mild diabetes	Yes	
5	Pancreatic atrophy renal dysplasia renal cysts renal insufficiency hypomagnesemia	Yes	Insulin
6		Yes	Insulin

- Most common type of MODY – MODY – 3 (HNF α – 1)

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Type 3 DM (3a, 3b, 3c)

- In certain individuals of Alzheimer's d/s there might be contributory insulin resistance
- Also called brain diabetes (3a)

Hall marks of type III diabetes

- Disturbed glucose homeostasis
  ↓
  GSK38, INS, IRS1, INSR IGF1R, AKT2
- Disturbed cell survival
  ↓
  BAD, BCL2, IL1K, CTSD
- Disturbed lipid metabolism
  ↓
  APOE, JAK-stat pathway
- Enhanced apoptosis
  ↓
  CASP8, CASP3, CDK5, P53 pathway

Type 4 DM

- Occurs in lean elderly individuals
- Insulin resistance (+)
- D/t defective T regulatory cells

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Drug induced Dm 00:52:06

- Certain drugs can lead to IGT & DM (Prediabetes)

Anti-infectives	
Fluoroquinolones	Gemifloxacin (Not available in united states)
HIV antiretrovirals	Protease inhibitors Nucleoside reverse transcriptase inhibitors (NRTI's)
Other anti-infectives	Pentamidine
Antipsychotics	
First generation	Chlorpromazine perphenazine other phenothiazines
Second generation	Clozapine iloperidone olanzapine paliperidone quetiapine risperidone
Cardiovascular	
Beta blockers	Atenolol metoprolol propranolol
Hypolipemic	Niacin (nicotinic acid) statins
Thiazide diuretics	Hydrochlorothiazide, chlorthalidone, chlorothiazide indapamide

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DIAGNOSIS OF DIABETES

Diagnosis of DM 00:00:17

- Fasting plasma glucose (8 hours fasting)
- 2hr plasma glucose
- HbA_1C (glycosylated hemoglobin) →
- Random plasma glucose → Don't rely
  - HbA_1C – indicates the control over last 2-3 months
  - S. fructosamine – control over last 2 weeks
- Normal → Pre-diabetes → Diabetes

↓

Impaired Glucose Tolerance (IGT)

Criteria for diagnosis of diabetes

- FPG ≥ mg/dl (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8h.

Or

- 2-h PG ≥ 200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.

Or

- A1C ≥ 6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.

Or

- In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dl (11.1 mmol/L)

Criteria defining prediabetes

- FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)

Or

- 2-h PG during 75g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)

Or

- A1C 5.7 – 6.4% (39 – 47 mmol/mol)

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Routine screening

- Asymptomatic

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Criteria for testing for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in adults with overweight or obesity (BMI ≥ 25 kg/m^2 or ≥ 23 kg/m^2 in Asian americans) who have one or more of the following risk factors:
   - First degree relative with diabetes
   - High risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)

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- History of CVD
- Hypertension (≥ 140/90 mmHg or on therapy for hypertension)
- HDL cholesterol level < 35 mg/dL (0.90 mmol/L) and/or a triglyceride level > 350 mg/dL (2.82 mmol/L)
- Women with polycystic ovary syndrome
- Physical inactivity
- Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)

2. Patients with prediabetes (A1C ≥ 5.7% [39 mmol/mol), IGT, or IFG) should be tested yearly.
3. Women who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other patients, testing should begin at age 45 years.
5. If results are normal, testing should be repeated at a minimum of 3 year intervals, with consideration of more frequent testing depending on initial results and risk status.
6. HIV

- HbA_1C – limitations

  ↓

  - Thalassemia
  - Anaemia

- CKD

Classification and Diagnosis of Diabetes

- A1C (continued)
  - In conditions associated with an altered relationship between A1C and glycemia, such as hemoglobinopathies including sickle cell disease, pregnancy (second and third trimesters and the postpartum period), glucose – 6- phosphate dehydrogenase deficiency, HIV, hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, only plasma blood glucose criteria should be used to diagnose diabetes.

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CHRONIC COMPLICATIONS OF DIABETES

Complications of DM
- Vascular
  - Microvascular
  - Macrovascular
- Non – Vascular
  ↓
  - Infections
  - Skin
  - Cataract

Diabetic Retinopathy. 00:03:56

- Microvascular complication
- Why?

  ↓

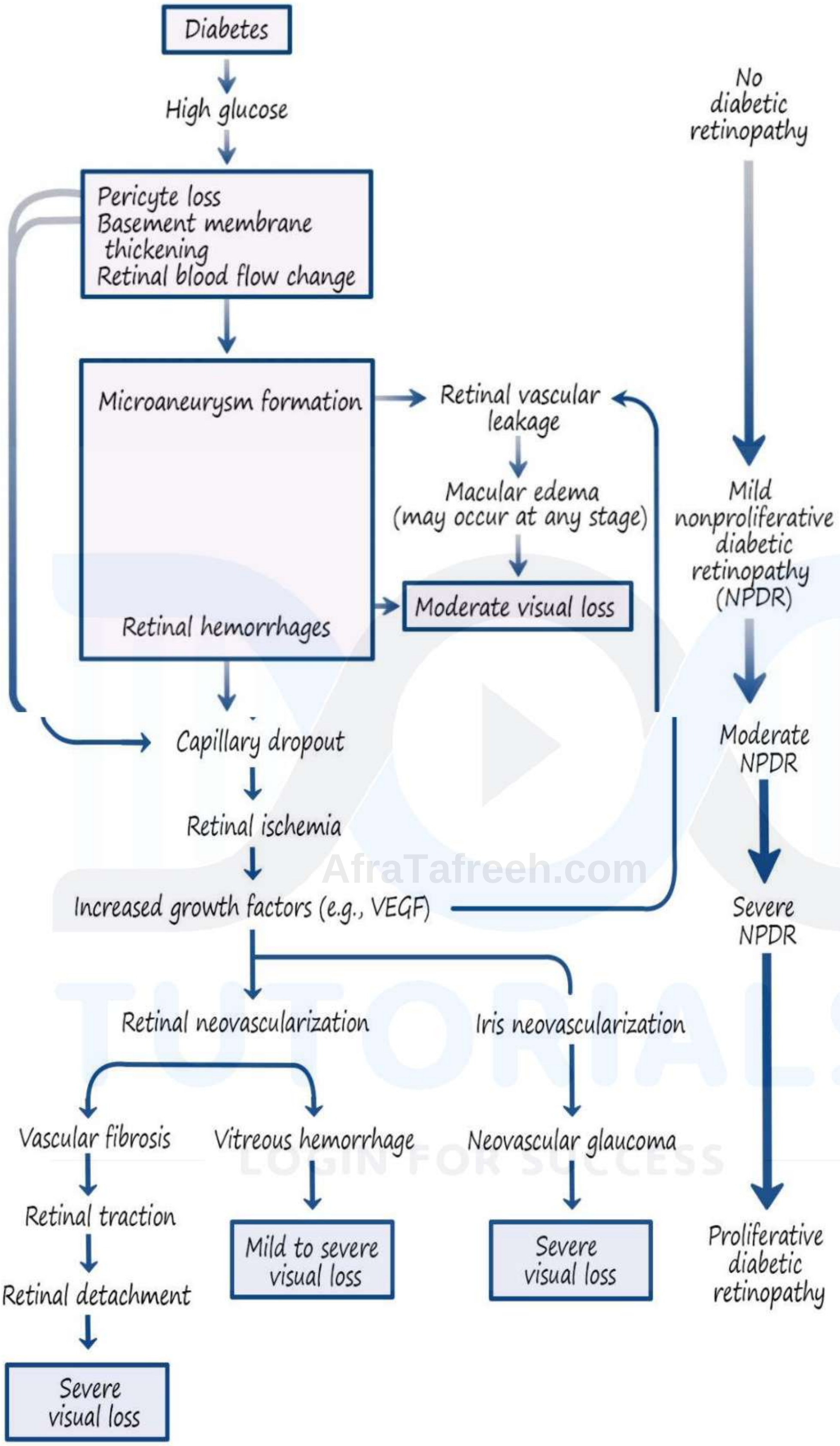
  when there is excess glucose → it is channeled to certain alternate pathways of metabolism

  ↓

  POLYOL PATHWAY
- Sorbitol → Fracture may cause AGE (Advanced glycosylation end products)

  ↓

  Retinopathy
- Polyol pathway is responsible for diabetic nephropathy as well.
- Diabetic retinopathy – 2 types
  - NPDR (Non proliferative diabetic retinopathy)
  - proliferative diabetic retinopathy



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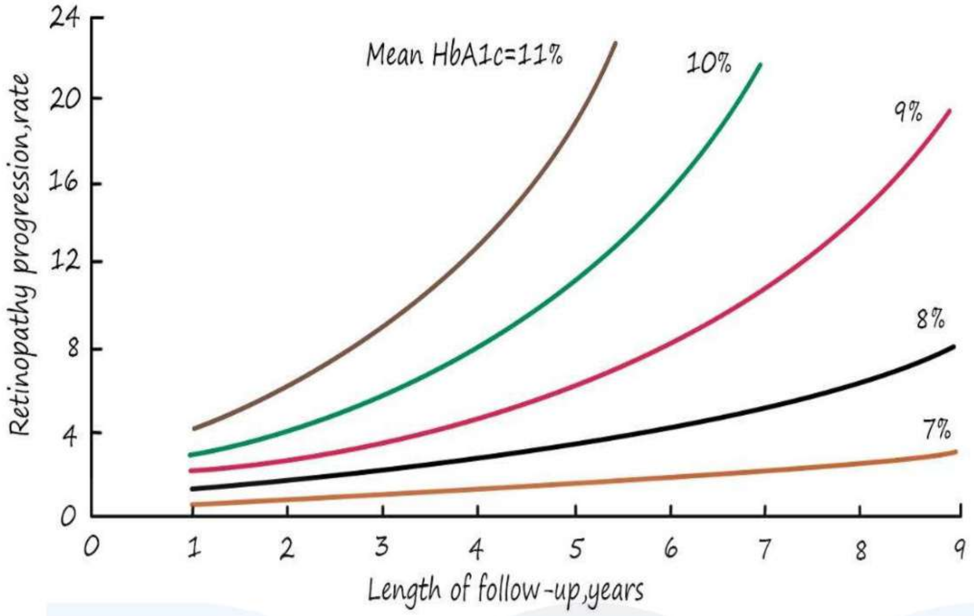

Diabetic Nephropathy. 00:16:08

- If diabetes not properly → end stage renal disease
- Microvascular complication
- Role of Age (Advanced glycosylated end products) is important.
- Diabetes affecting kidney can affect glomerulus and tubules
- As diabetes progresses → albuminuria

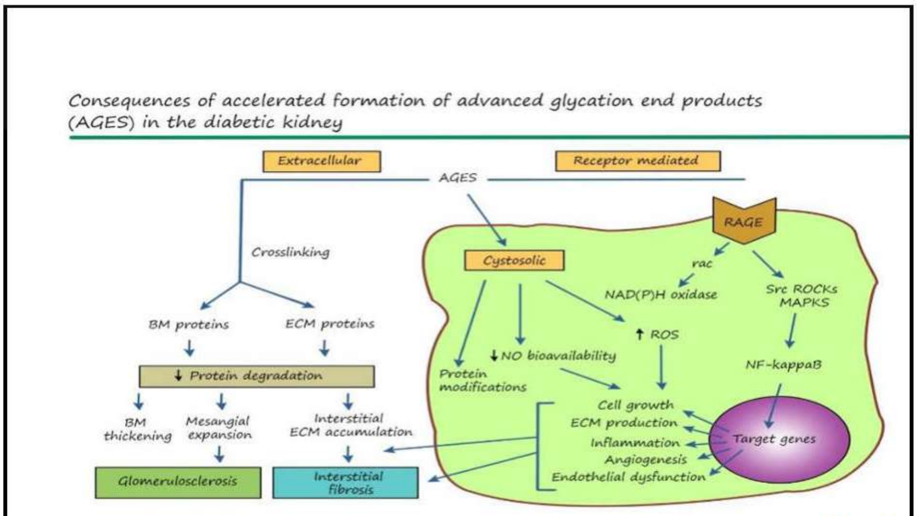

Fig: 1

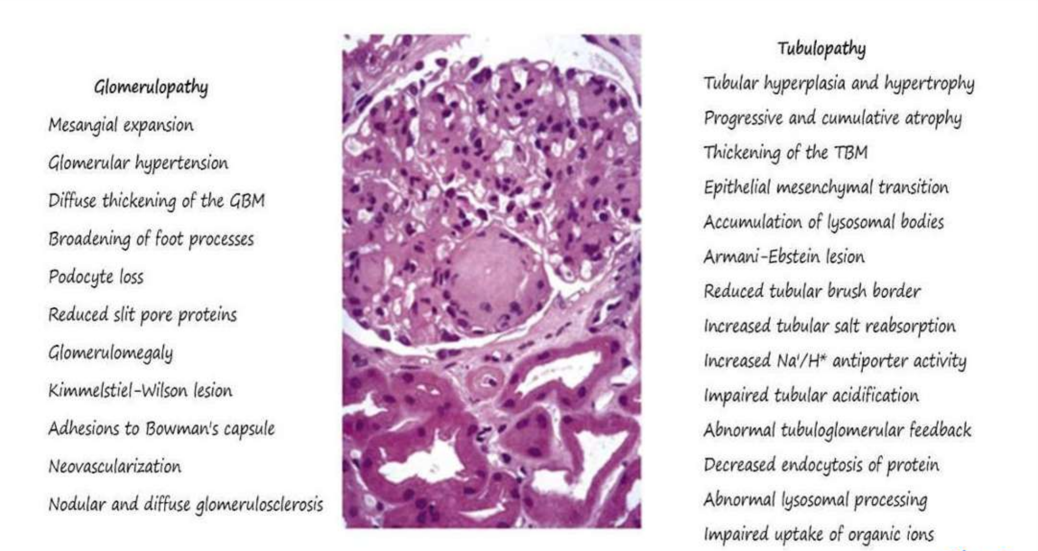

Fig: 2

- Treatment – Laser photocoagulation
  Anti VEGF agents

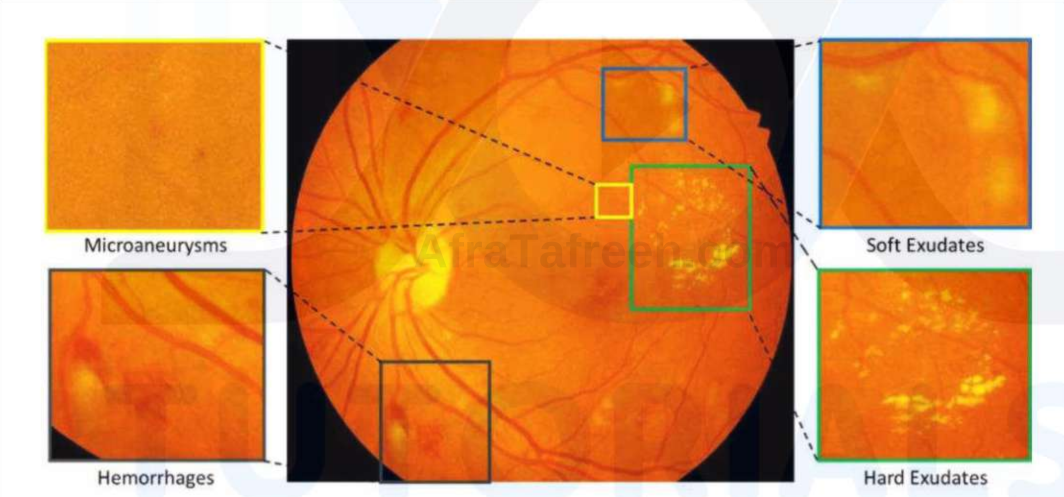

Fig: 3

LOGIN FOR SUCCESS

Diabetic Maculopathy

- Diabetic macular edema: Appearance on optical coherence tomography

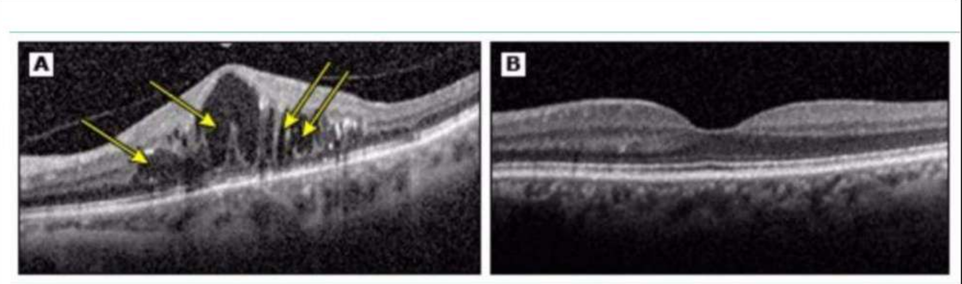

Fig: 4

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A. Optical coherence tomography (OCT) of diabetic macular edema. There are numerous large cysts visible within the macula (arrows), and the retinal thickness is increased.

B.OCT of normal macula (for comparison) showing typical foveal contour.

Screening of Retinopathy

Schedule

Patient group	Recommended first examination	Minimum routine follow-up
Type 1 diabetes	Within 5 years after diagnosis of diabetes once patient is age 10 years or older.	Yearly, if retinopathy present Every 2 years if there is no evidence of retinopathy
Type 2 diabetes	At time of diagnosis of diabetes.	Yearly, if retinopathy present Every 2 years if there is no evidence of retinopathy

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Pregnancy in preexisting diabetes	Prior to conception and during first trimester. Counsel on the risk of development and/or progression of retinopathy	Close foloow-up throughout pregnancy and for 1 year postpartum.

- Glomerular HTN
  ↓
  Stage of hyperfiltration → Increases GFR

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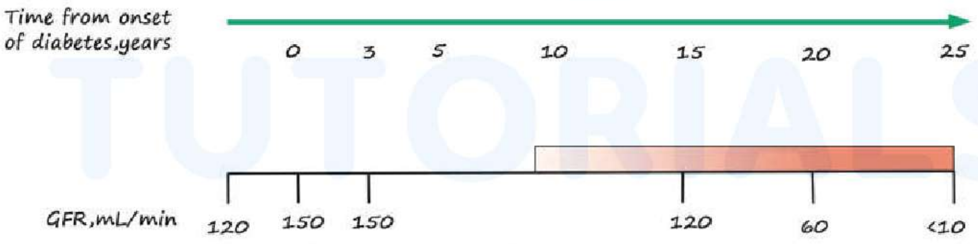

- Time course of development of diabetic nephropathy. The relationship of time from onset of diabetes, albuminuria, and the glomerular filtration rate (GFR) are shown.

Diabetic Neuropathy

- Most common macrovascular comp – CAD
- Neuropathy

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- Sensory and motor (mono-and polyneuropathy)
- Autonomic

- Nephropathy (albuminuria and declining renal function)
- Macrovascular
  - Coronary heart disease
  - Peripheral arterial disease
  - Cerebrovascular disease
- Other
  - Gastrointestinal (gastroparesis, diarrhea)
  - Genitourinary (uropathy/sexual dysfunction)
  - Dermatologic
  - Infectious
  - Cataracts
- Cheiroarthropathy

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MANAGEMENT OF DM

Management of DM 00:00:30

Management of Type 2 Diabetes

Individualized glycemic control
- Diet/lifestyle
- Exercise
- Medication

Treat associated conditions
- Dyslipidemia
- Hypertension
- Obesity

Screen for/manage complications of diabetes
- Retinopathy
- Nephropathy
- Neuropathy
- Cardiovascular disease
- Other complications

Treatment Goals 00:05:24

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Index	Goal
• Glycemic control HbA_{1C} Preprandial capillary plasma Glucose Postprandial capillary plasma Glucose[d]	<7.0% 4.4–7.2 mmol/L (80–130 mg/dL) <10.0 mmol/L (<180 mg/dL)
• Blood pressure	<140/90 mmHg[e]

- 10.4 For individuals with diabetes and hypertension at higher cardiovascular risk (existing atherosclerotic cardiovascular disease or 10 – year atherosclerotic cardiovascular disease risk >25%), a blood pressure target of <130%/80mmHg may be appropriate, if it can be safely attained.

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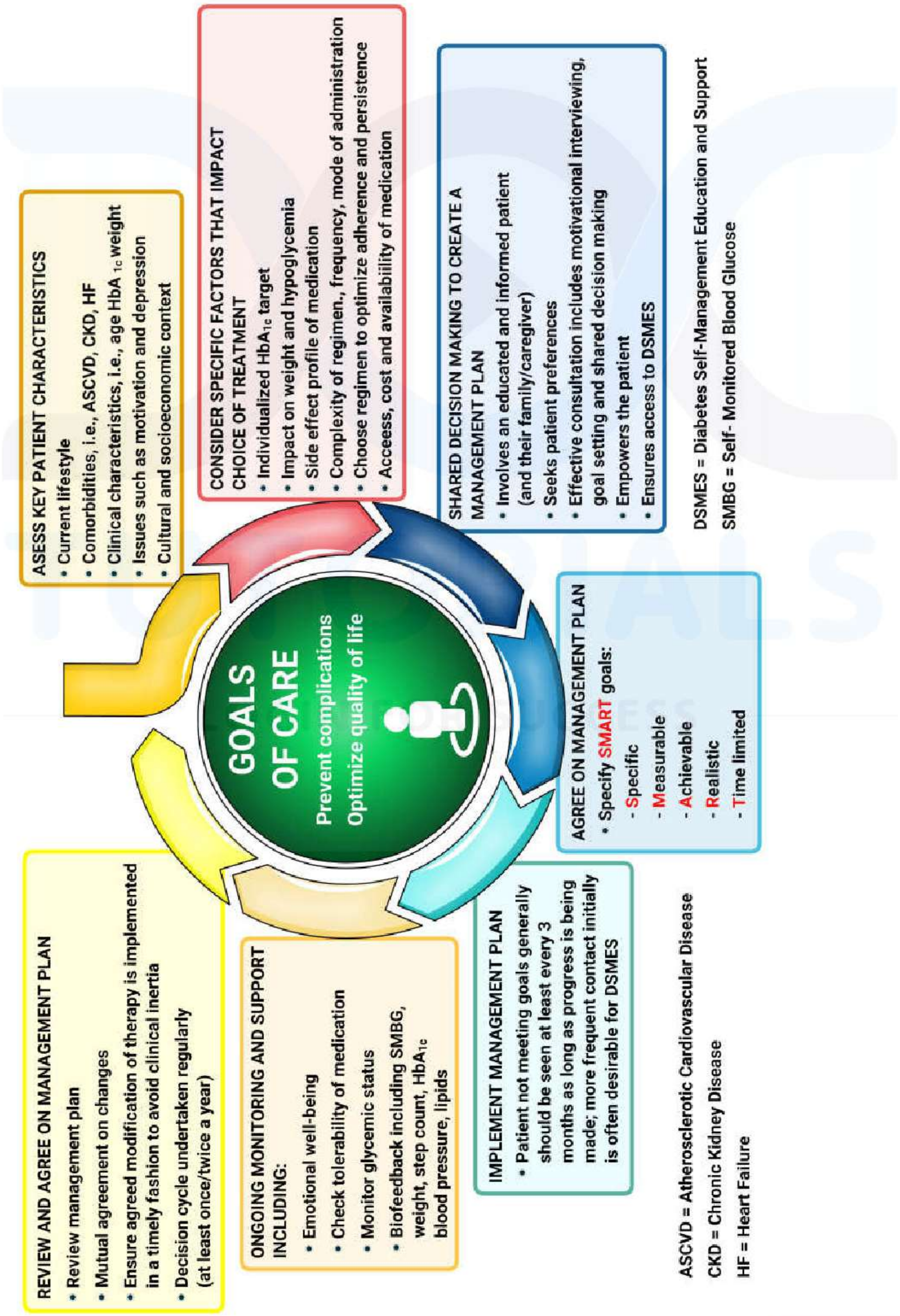
Cholesterol targets 00:08:16

- LDL < 100 mg%

  < 70mg %
- HDL > 50 mg% (Females)

  > 40 mg% (males)
- TG < 150 mg%
- Management – patient centric



Balanced diet

- Carbohydrates – (50-65%)
  ↓
  - Low glycemic index (oats)
  - Prefer complex carbohydrates (Roti, legumes, whole grain)
  - Increases frequency, Decreases quantity
- Proteins – 1g/kg/day (15-20%)
  CKD – 0.8g/kg/day
- Lipids (15-25%)
  - <10% saturated fat
  - LDL > 100 - <7% of saturated fat
  - No transfats
- Vegetables
- Dietary fiber
- Salt <5g/day → No pickles, No pappads
- No sweets, No sweetened beverages
- Fruits – Avoid Mango
  Pine apple
  Jack fruit
  - Should be taken between 2 major meals.

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Exercise

- 30 mins of light aerobic exercise daily for 5 days (jogging, brisk walking)
- Increases Glucose uptake by muscle
- Weight reduction → Decreases Insulin resistance (central obesity)

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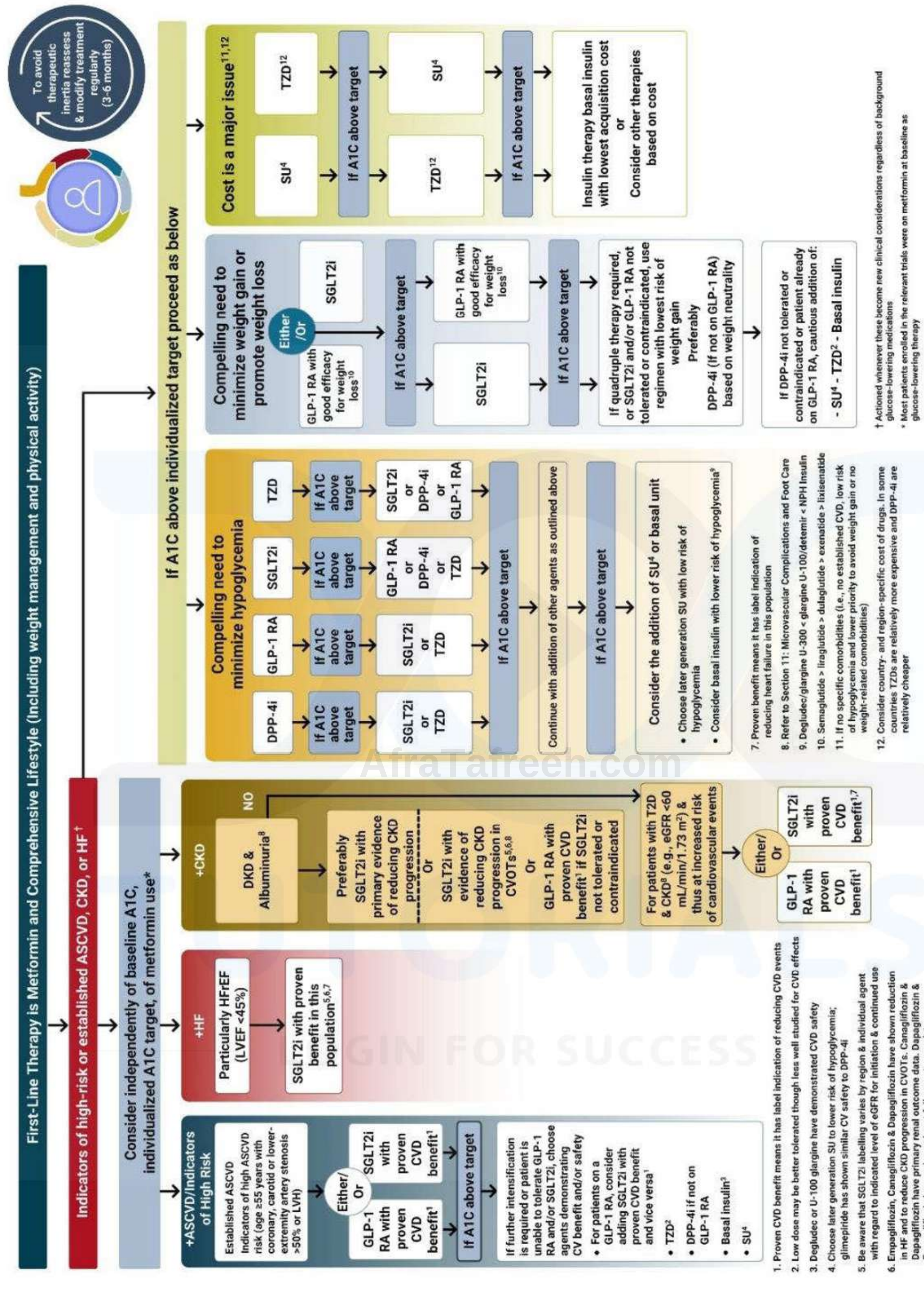
Pharmacotherapy

OHA → Insulin

- In scenarios of DKA/Hyperosmolar coma, type I DM
  ↓
  Start with insulin
- If HbA1c > 9 → Insulin

OHA

- 1st choice – Biguanides – Metformin
  ↓
  - Decreases hepatic glucose production
  - Increases peripheral utilization of glucose by upregulating GLUT-4 receptors.
  - Decreases insulin resistance
  - Dose – 500mg 1-0-1
    ↓
    Increased up to 2.5g/day
  - ADR – Lactic acidosis
  - If GFR < 30ml/min, 30-45 ml/min
    ↓
    metformin not started
    - Vit B_{12} deficiency.
  - Adv – Does not cause hypoglycemia weight neutral/modest weight loss.
  - Causes HbA1C reduction of 1-2%


First-Line Therapy is Metformin and Comprehensive Lifestyle (Including weight management and physical activity)
Indicators of high-risk or established ASCVD, CKD, or HF†
Consider independently of baseline A1C, individualized A1C target, of metformin use*
+ASCVD/Indicators of High Risk
Established ASCVD
Indicators of high ASCVD risk (age ≥55 years with coronary, carotid or lower-extremity artery stenosis >50% or LVH)
GLP-1 RA with proven CVD benefit1
Either/Or
SGLT2i with proven CVD benefit1
If A1C above target
If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety
• For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit and vice versa1
• TZD2
• DPP-4i if not on GLP-1 RA
• Basal insulin3
• SU4
+HF
Particularly HFrEF (LVEF <45%)
SGLT2i with proven benefit in this population5,6,7
+CKD
DKD & Albuminuria8
NO
Preferably SGLT2i with primary evidence of reducing CKD progression
Or
SGLT2i with evidence of reducing CKD progression in CVOTs5,6,8
Or
GLP-1 RA with proven CVD benefit1 if SGLT2i not tolerated or contraindicated
For patients with T2D & CKD8 (e.g., eGFR <60 mL/min/1.73 m2) & thus at increased risk of cardiovascular events
GLP-1 RA with proven CVD benefit1
Either/Or
SGLT2i with proven CVD benefit1,7
If A1C above individualized target proceed as below
Compelling need to minimize hypoglycemia
DPP-4i
GLP-1 RA
SGLT2i
TZD
If A1C above target
SGLT2i or TZD
SGLT2i or TZD
GLP-1 RA or DPP-4i or TZD
SGLT2i or DPP-4i or GLP-1 RA
If A1C above target
Continue with addition of other agents as outlined above
If A1C above target
Consider the addition of SU4 or basal unit
• Choose later generation SU with low risk of hypoglycemia
• Consider basal insulin with lower risk of hypoglycemia9
Compelling need to minimize weight gain or promote weight loss
GLP-1 RA with good efficacy for weight loss10
Either/Or
SGLT2i
If A1C above target
SGLT2i
GLP-1 RA with good efficacy for weight loss10
If A1C above target
If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain
Preferably
DPP-4i (if not on GLP-1 RA) based on weight neutrality
If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:
- SU4 - TZD2 - Basal insulin
Cost is a major issue11,12
SU4
TZD12
If A1C above target
TZD12
SU4
If A1C above target
Insulin therapy basal insulin with lowest acquisition cost
or
Consider other therapies based on cost
To avoid therapeutic inertia reassess & modify treatment regularly (3-6 months)
1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region & individual agent with regard to indicated level of eGFR for initiation & continued use
6. Empagliflozin, Canagliflozin & Dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data. Dapagliflozin & Empagliflozin have primary heart failure outcome data
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec/glargine U-300 < glargine U-100/detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper
† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications
* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy

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	Mechanism of Action	Examples	HBA$_{1c}$ reduction (%)
Oral			
Biguanides	Decreases hepatic glucose production	Metformin	1-2
α – Glucosidase inhibitors	Decreases GI glucose absorption	Acarbose, miglitol, voglibose	0.5-0.8
Dipeptidyl peptidase IV inhibitors	Prolong endogenous GLP-1 action; Increases insulin, decreases glucagon	Alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin	0.5-0.8
Insulin secretagogues: sulfonylureas	Increases insulin secretion	Glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glyburide, glyclopyramide	1-2
Insulin secretagogues: Non sulfonylureas	Increases insulin secretion	Mitiglinide nateglinnide, repaglinide	0.5-1.0
Sodium- glucose cotransporter 2 inhibitor	Increases glucose excretion	Canagliflozin, dapagliflozin, empagliglozin, ertugliflozin	0.5-1.0
Thiazolidinediones	Decreases insulin resistance, Increases glucose utilization	Pioglitazone, rosiglitazone	0.5-1.4

	Agent – specific advantages	Agent – specific Disadvantage	Contraindications
Oral			
Biguanides	Weight neutral, do not cause hypoglycemia, inexpensive, extensive, Decreases CV events	Diarrhea, nausea, lactic acidosis, vitamin B12 deficiency	Renal insufficiency (see text for GFR <45 mL/min), CHF, radiographic contrast studies, hospitalized patients, acidosis
α – Glucosidase inhibitors	Reduce postprandial glycemia	GI flatulence, liver function tests	Renal/liver disease
Dipeptidyl peptidase IV inhibitors	Well, tolerated, do not cause hypoglycemia	Angioedema/ urticarial and immune – mediated dermatologic effects	Reduced dose with renal disease
Insulin secretagogues: sulfonylureas	Short onset of action, lower postprandial glucose, inexpensive	Hypoglycemia, weight gain	Renal/liver disease
Insulin secretagogues: Non sulfonylureas	Short onset of action, lower postprandial glucose	Hypoglycemia	Renal/liver disease
Sodium- glucose cotransporter 2 inhibitor	Do not cause hypoglycemia, decrease weight and BP; see text for CVD effect	Urinary and genital infections, polyuria, dehydration, exacerbate tendency to hyperkalemia and DKA; see text	Moderate renal insufficiency, insulin deficient DM
Thiazolidinediones	Lower insulin requirements	Peripheral edema, CHF, weight gain, fractures, macular edema	CHF, liver disease

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- Thiazolidinediones
  - PPAR γ agonist
  - Increased risk of bladder Ca (but not proved)
- GLP-1 receptor agonist
  - Incretin based therapy
  - Given subcutaneously
  - Drugs
    ↓
    Liraglutide
    Semaglutide
- DPP-4 Inhibitors
  - Dipeptidyl peptidase inhibitors
  - Gliptins
- $SGLT_2$ Inhibitors
  - Acting on proximal convoluted tubule and inhibiting reabsorption glucose → Glucosuria
  - Canagliflozin
  - Dapagliflozin
  - Empagliflozin

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Parenteral			
Amylin agonists	Slow gastric emptying, Decreases glucagon	Pramlintide	0.25-0.5
GLP-1 receptor agonists	Increases insulin, decreases glucagon, slow gastric emptying, satiety	Albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide	0.5-1.0
Insulin	Increases Glucose utilization, Decreases hepatic glucose production, and other anabolic actions	See text and table 397-4	Not limited

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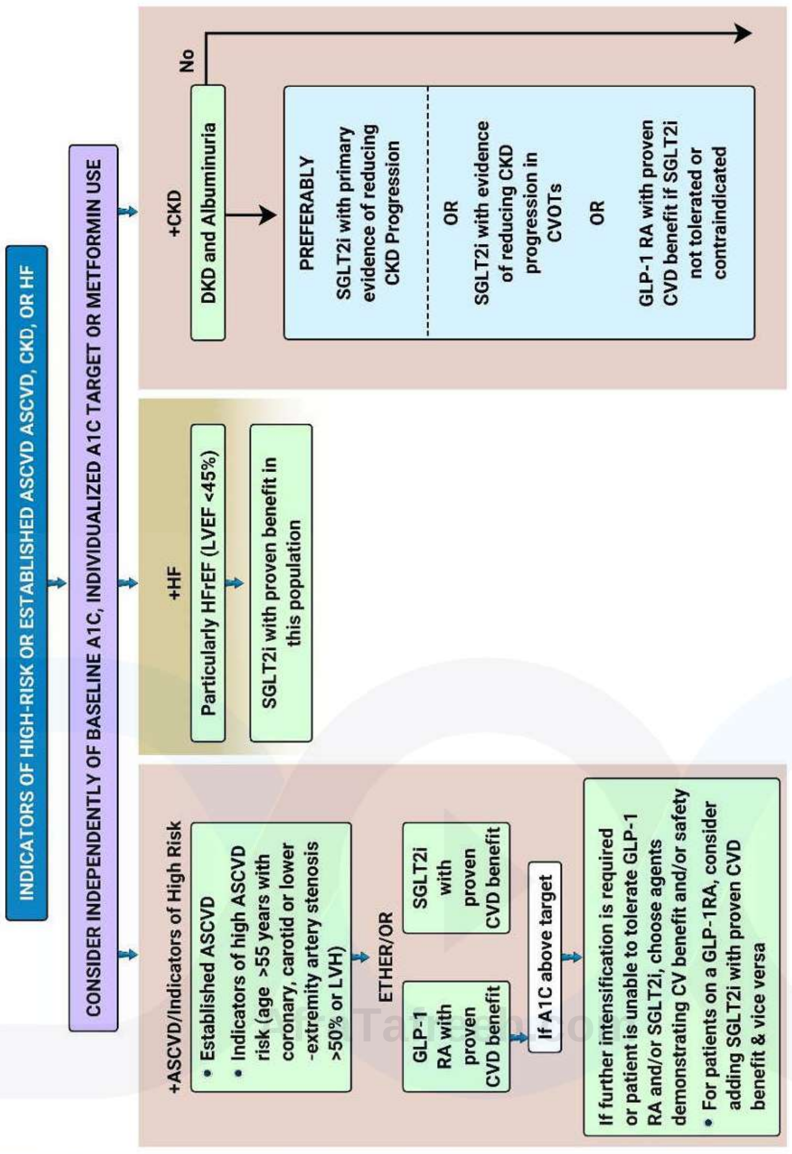
Parenteral			
Amylin agonists	Reduce postprandial glycemia, weight loss	Injection, nausea, Increases risk of hypoglycemia with insulin	Agents that also show GI motility
GLP-1 receptor agonists	Weight loss, do not cause hypoglycemia; see text for CVD effect	Injection, nausea, Increases risk of hypoglycemia with insulin secretagogues	Renal disease, agents that also slow GI motility; medullary carcinoma of thyroid, pancreatic disease
Insulin	Known safety profile	Injection, weight gain, hypoglycemia	


INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD ASCVD, CKD, OR HF
CONSIDER INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET OR METFORMIN USE
+ASCVD/Indicators of High Risk
• Established ASCVD
• Indicators of high ASCVD risk (age >55 years with coronary, carotid or lower -extremity artery stenosis >50% or LVH)
ETHER/OR
GLP-1 RA with proven CVD benefit
SGLT2i with proven CVD benefit
If A1C above target
If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety
• For patients on a GLP-1RA, consider adding SGLT2i with proven CVD benefit & vice versa
+HF
Particularly HFrEF (LVEF <45%)
SGLT2i with proven benefit in this population
+CKD
DKD and Albuminuria
No
PREFERABLY
SGLT2i with primary evidence of reducing CKD Progression
OR
SGLT2i with evidence of reducing CKD progression in CVOTs
OR
GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

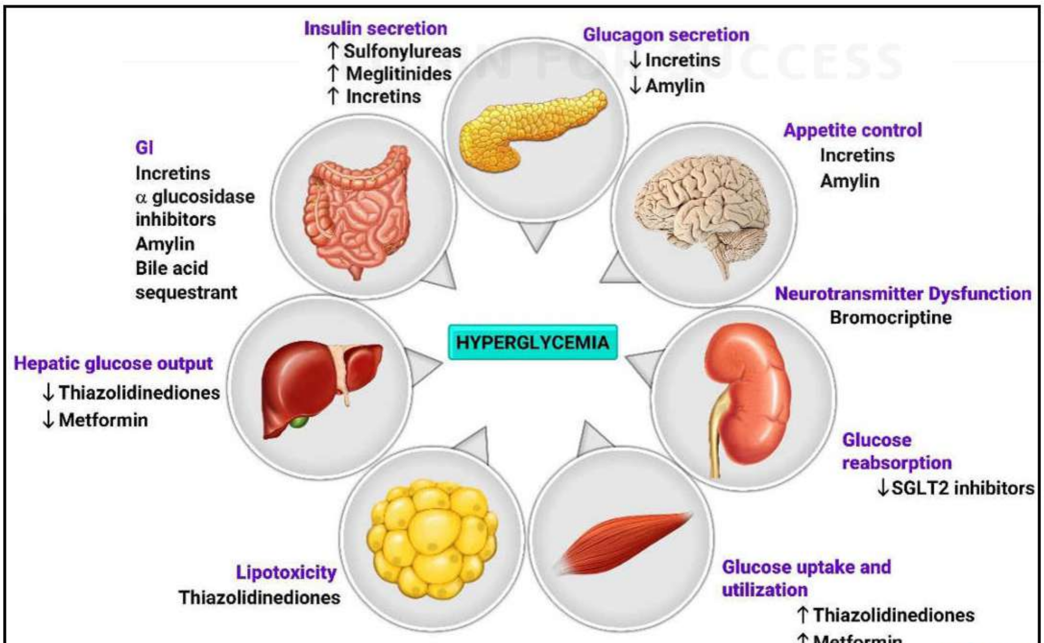

Insulin secretion
↑ Sulfonylureas
↑ Meglitinides
↑ Incretins
Glucagon secretion
↓ Incretins
↓ Amylin
Appetite control
Incretins
Amylin
Neurotransmitter Dysfunction
Bromocriptine
Glucose reabsorption
↓ SGLT2 inhibitors
Glucose uptake and utilization
↑ Thiazolidinediones
↑ Metformin
Lipotoxicity
Thiazolidinediones
Hepatic glucose output
↓ Thiazolidinediones
↓ Metformin
GI
Incretins
α glucosidase inhibitors
Amylin
Bile acid sequestrant
HYPERGLYCEMIA

Fig: 1

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Insulin Therapy in Diabetes 01:12:30

Indications

i. Type 2 DM not controlled with DHA

ii. Type 1 DM

iii. Diabetic ketoacidosis

iv. Non ketotic hyperosmolar coma

v. Stressful conditions

- Surgery (perioperative period)
- Stroke
- MI
- Infection
- Pregnancy

Insulin preparations

Ultra-short acting (s/c)	Short acting (s/c i.v)	Intermediate acting	Long acting
↓	↓	↓	↓
- Lispro - Aspart - Glulisine	Regular insulin	- Neutral - Portamine - Hegedorn (NPH)	- Glargine - Detemer - Degludec. ↓ Peakless insulin

ACUTE COMPLICATION DM

Acute Complication of DM 00:00:21

i. Diabetic Ketoacidosis

ii. Hyperglycaemic Hyperosmolar state (HHS)

(OR)

HONK – Hyperosmolar non – Kenotic coma

DKA	HHS
Most common In type I DM	Most common In type II DM

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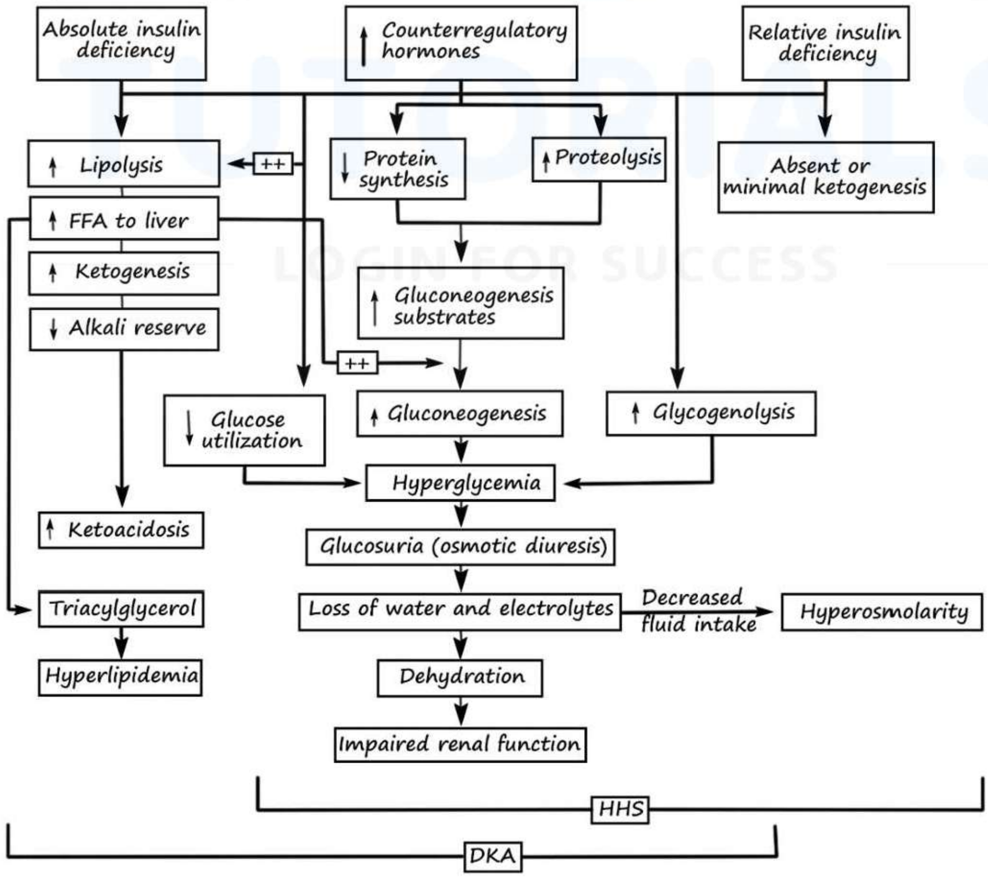
Pathogenesis 00:02:56



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- Hyperglycaemia
  - Because of insulinogenic, tissue utilization of glucose is not happening

    ↓

    Depends on other sources for energy
- Acetyl co A → TCA cycle

  ↓

  Increased

  ↓

  Ketone body synthesis

  ↓

  Acetoacetate

  Acetone

  Beta Hydroxy butyrate

- Hyperglycaemic State

  ↓

  Increased in counter regulatory hormone
  - Glucagon
  - Growth hormone
  - Catecholamines

Tissues are not able to utilize glucose because of insulinogenic

↓

Increases counter regulatory hormones

- DKA – Increases osmolality
- HHS – ↑↑↑ Osmolality

  ➔ Incidence of Cerebral edema – more in children

DKA

- Triggers of DKA
  - i. Poor complication with insulin
  - ii. Infection
  - iii. CVA
  - iv. ACS – MI
  - v. Cocaine
  - vi. Pregnancy

Clinical Feature

i. Nausea vomiting
ii. Abdominal Pain
iii. Features of dehydration → Hypovolemic Shock
iv. Altered sensorium, Stupor, Coma

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Manifestations of Diabetic Ketoacidosis	
• Symptoms – Nausea/vomiting – Thirst/polyuria – Abdominal pain – Shortness of breath • Precipitating events – Inadequate insulin administration – Infection (Pneumonia/UTI/ gastroenteritis/ sepsis) – Infarction (cerebral, coronary, mesenteric, peripheral) – Drugs (Cocaine) – Pregnancy	• Physical findings – Tachycardia – Dehydration/ hypotension – Tachypnea/ Kussmaul respiration/ respiratory distress – Abdominal tenderness (may resemble acute pancreatitis or surgical abdomen) – Lethargy/obtundation/ cerebral edema/possibly coma

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- Rapid acidotic breathing → Kussmaul's breathings
- Fruity odor – Acetone

Investigations

- RBS ↑↑ (>250 mg%)
- Urine ketone body – Rothera's test

  ↓

  Acetoacetate are detected
- Plasma osmolality will be high (300 – 320 mosm/kg)
- Hypertonic Hyponatremia
- Acidosis → Redistribution of body potassium, so that the potassium which predominantly a intracellular cation will come to extracellular space

  ↓

  Hyperkalemia
- Hyperphosphatemia
- ABG: - PH decreases

  PCO_2 wash out would be there

  ↓

  PCO_2 decreases

  ↓

  HCO_3
- Look at WBC count – Infection
- RFT – AKI

Treatment

- Endocrine emergency

  I. Fluid Replacement – Corner stone of management

  - Around 6L of fluids loss would be there → 3L ECF, 3L ICF
  - Fluid of Choice – NS
  - RL – not preferred
  - Aggressive fluid replacement except CAD

Volume status

- Severe hypovolemia ↓ Administer 0.9% NaCL (1.0 L/hour)
- Mild hypovolemia ↓ Evaluate corrected serum Na ↓ Determine hydration status
  - Serum Na high / Serum Na Normal → 0.45% NaCL (250 to 500 mL/hour) depending on volume state
  - Serum Na low ↓ 0.9% NaCl (250 to 500 mL/hour) depending on volume state
- Cardiogenic shock ↓ Hemodynamic monitoring/pressors

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When serum glucose reaches 200 mg/dL, change to 5% dextrose with 0.45% NaCl at 150 to 250 mL/hour

↓

- Check electrolytes, BUN, venous pH, creatinine, and glucose every two to four hours until stable.

- 1 litre fluid / Hour

  ↓

  Monitor electrolytes 2nd hourly

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II. Insulin

- Bolus – 0.1 units/ kg
- Infusion – 0.1 unit/kg/Hour

(Regular Insulin)

Insulin

IV route
↓
Insulin: Regular 0.1 units.kg as IV bolus
↓
0.1 units/kg/hour IV continuous insulin infusion

Uncomplicated DKA-SC route
↓
Rapid-acting insulin: 0.3 units/kg, then 0.2 units/kg one hour later
↓
Rapid acting insulin: 0.2 units/kg SC every two hours

↓

If serum glucose does not fall by 50 to 70 mg/dL in first hour, double IV or SC insulin bolus

↓

When serum glucose reaches 200 mg/dL, reduce regular insulin infusion to 0.02 to 0.05 units/kg/hour IV, or give rapid-acting Insulin at 0.1 units/kg SC every two hours
Keep serum glucose between 150 and 200 mg/dL until resolution of DKA

↓

- Check electrolytes, BUN, venous pH, creatinine, and glucose every two to four hours until stable
- After resolution of DKA and when patient is able to eat, initiate SC multidose (basal-bolus) insulin regimen
- Continue IV insulin infusion for two to four hours after SC insulin begun to ensure adequate plasma insulin levels.
- In insulin naïve patients, start at 0.5 to 0.8 units/kg body weight per day, and adjust insulin as needed
- Look for precipitating cause(s)

- Plain insulin action starts 30-45 Minutes after administration
  ↓
  Hence there should

APPROACH TO PROTEINURIA

Approach 00:00:26

- Protein in Normal healthy individual - <150 mg/day
- Proteins in Normal
  - Tamm Horsfall protein (most common)
  - Albumin (< 30mg/day)
  - Urokinase
  - Secretory IgA
  - β_2 microglobulin .

Classification

- Based on mechanism
  - Glomerular source
  - Tubular
  - Overflow proteinuria – Too much supply of proteins
  - Orthostatic proteinuria - < 30 years of age (rare)
  - Post renal inflammation
  - Transient proteinuria

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Classification or proteinuria	Clinical setting	Typical level of proteinuria in adults
Transient proteinuria	Fever, heavy exercise, vasopressor infusion, albumin infusion	< 1g/day

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Persistent proteinuria – orthostatic proteinuria	Uncommon over age 30 years, may occur in 2 to 5 percent of adolescents	< 1 to 2g/day
Persistent proteinuria – overflow proteinuria	Myeloma (monoclonal light chains), hemolysis (hemoglobinuria), rhabdomyolysis (myoglobinuria)	Variable, could be nephrotic range
Persistent proteinuria – glomerular proteinuria	Primary glomerular disease, secondary glomerular disease, diabetic nephropathy, hypertensive nephrosclerosis	Variable, often nephrotic range
Persistent proteinuria – tubulointerstitial proteinuria	Heavy metal intoxications autoimmune or allergic interstitial inflammation, medication induced interstitial injury	< 3g/day
Post-renal proteinuria	Urinary tract infection, nephrolithiasis, genitourinary tumor	<1 g/day

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- Based on color change in dipstick method, proteinuria may be
  - Trace
  - 1+
  - 2+
  - 3+

- In dipstick method, only albumin is estimated
- Negative dipstick test does not rule out proteinuria completely
- Other test for protein → sulfasalicylic acid test
  ↓
  Total protein test
- Microalbuminuria – not picked up .

- Quantitative assessment
  ↓
  - 24 hour urinary protein estimation
  - PCR – protein creatinine ration – spot urine sample
    ↓
    $$\frac{\text{mg protein}}{\text{gram urinary creatinine}} = \text{mg/24 hours}$$
  - Albumin creatinine ratio (ACR) - better test
    $$\frac{\text{mg. albumin}}{\text{gram urinary creatinine}} = \text{mg/24 hours}$$

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DOC TUTORIALS
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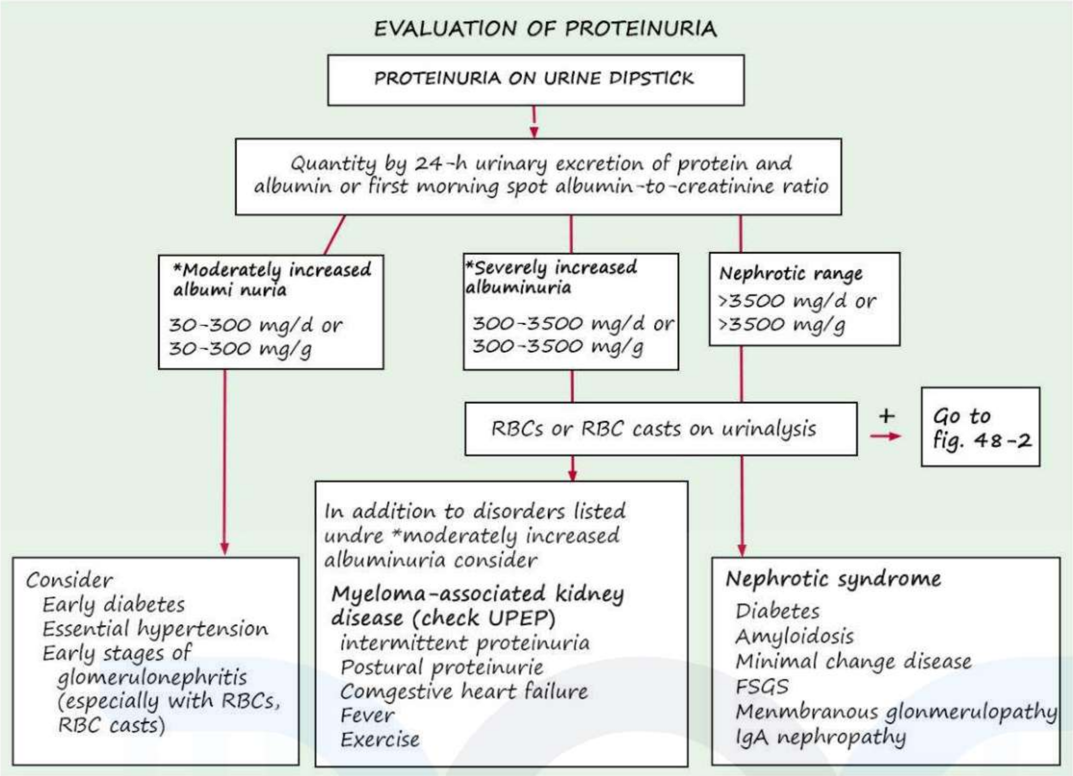

- Term microalbuminuria is replaced by moderately increased albuminuria
- Minimal change d/s – selective proteinuria (mostly albumin in urine)

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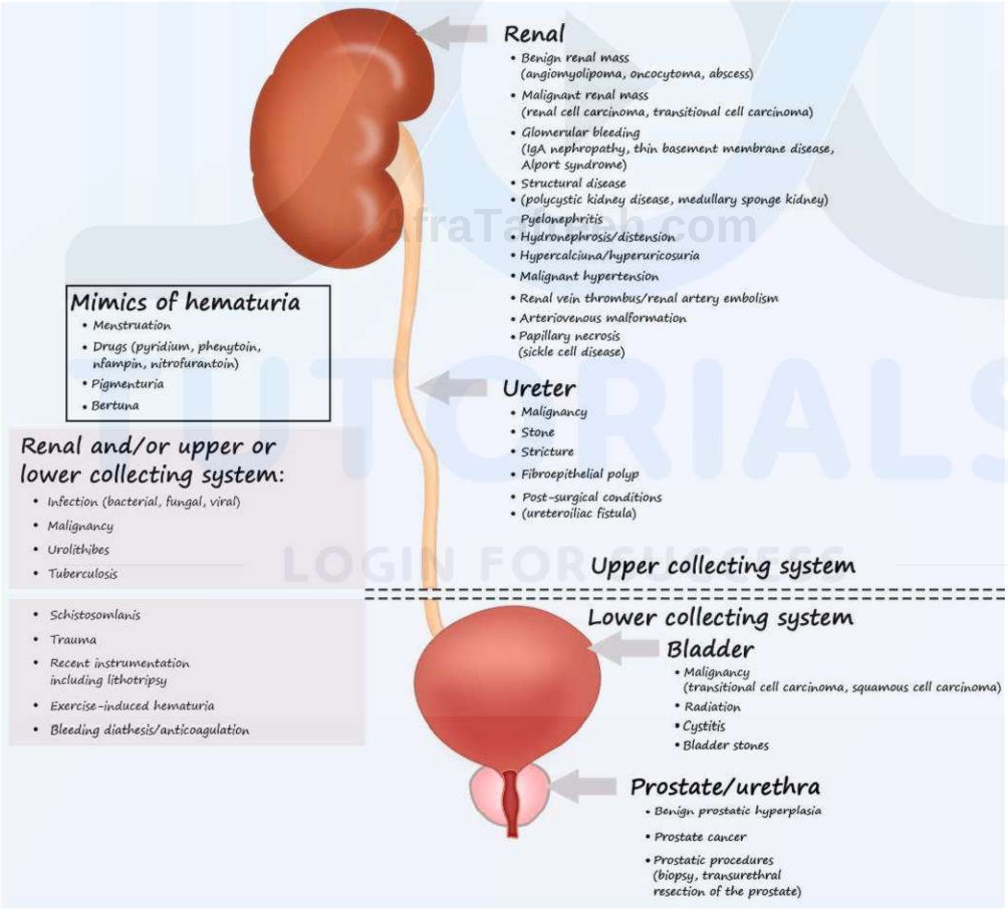
APPROACH TO HEMATURIA

Approach 00:00:27

- N urine – 1 or 2 RBC's/hpF
- Signigicant hematuria
  - ≥ 3 RBC's/hpF of centrifuged urine sample on 3/more occasions
  - 100 RBC's/hpF in a single urine sample

    (or)

    Gross hematuria



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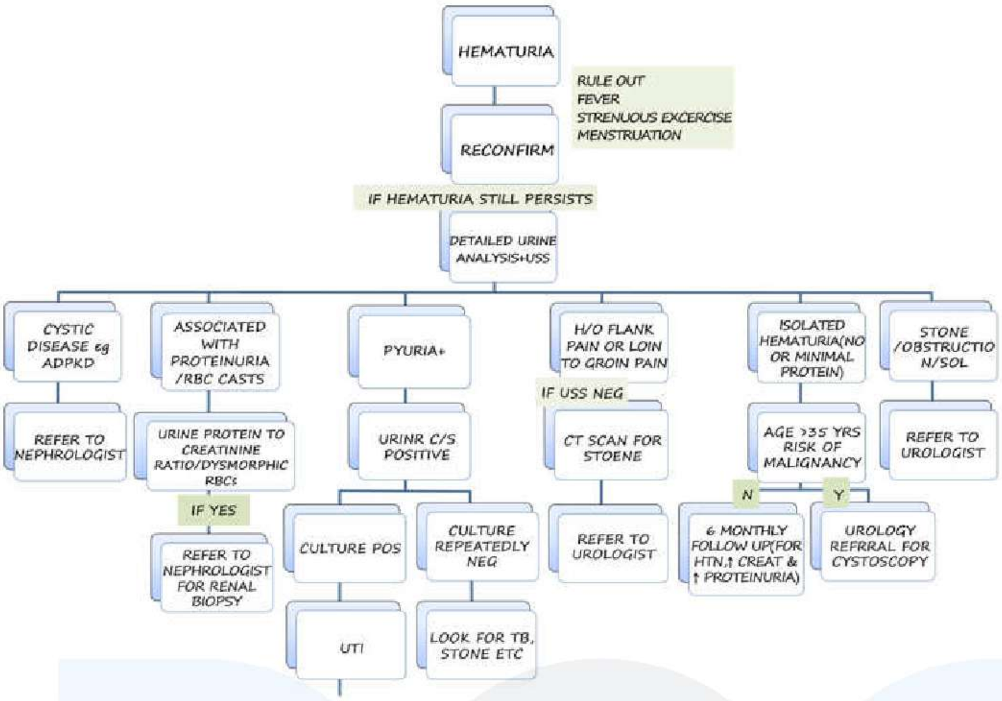
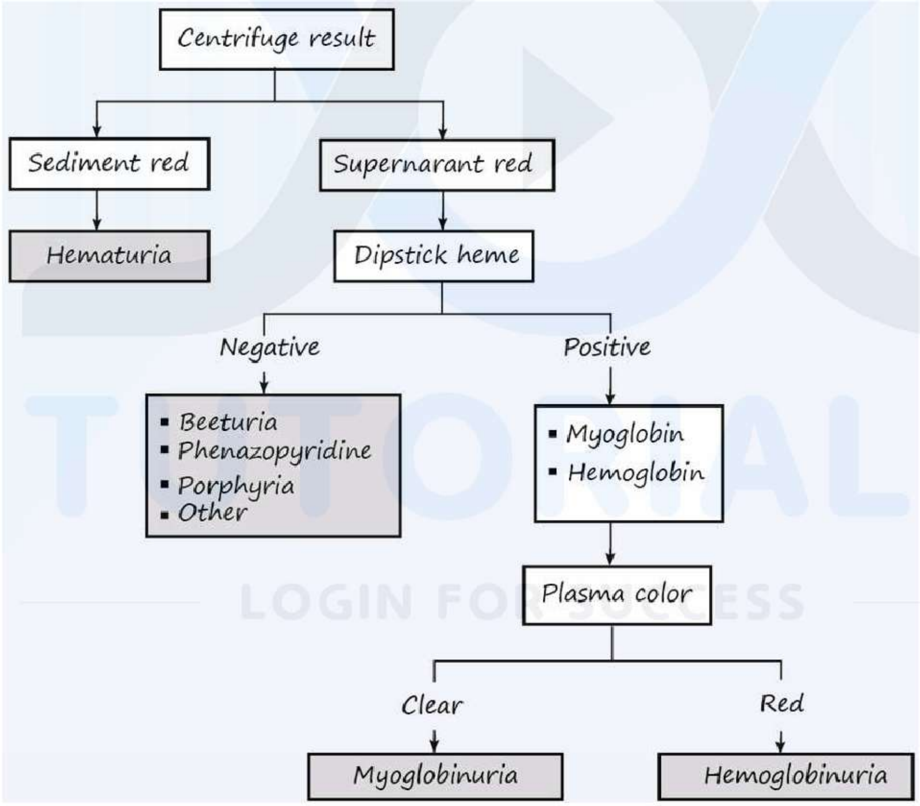
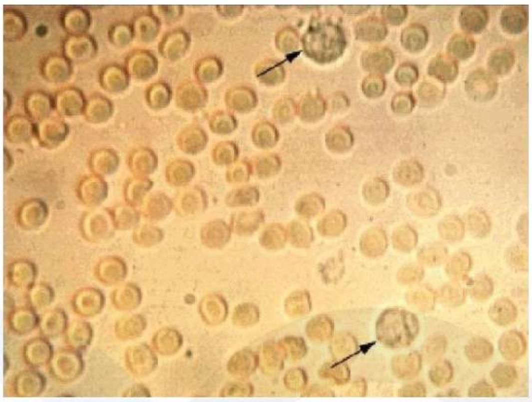




- Dipstick test – based on peroxidase activity of Hb
- Glomerular origin hematuria
  - ≥ Dysmorphic RBC's
  - ≥ 5% acanthocytes
  - RBC cast, proteinuria > 500mg/day

- No blood clots
- Color – Cola colored urine (acid pH → acid hematin)

Phase contrast micrograph:



Isomorphic/Monomorphic RBC

Fig: 1

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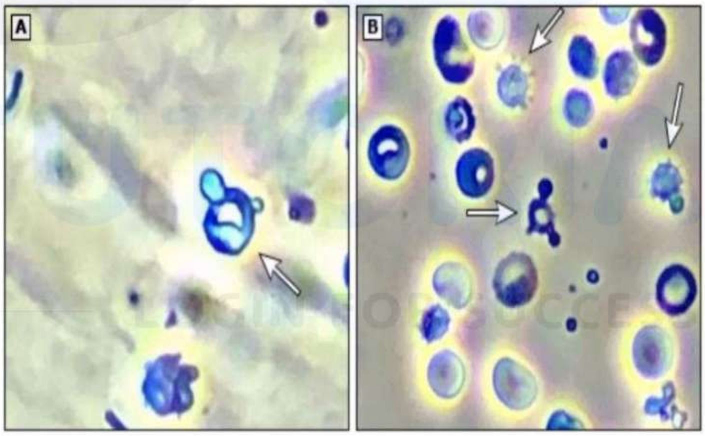

Scanning electron micrograph:

Dsymorphic RBC's

Fig: 2

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40% Dysmorphic + 5% acanthocytic

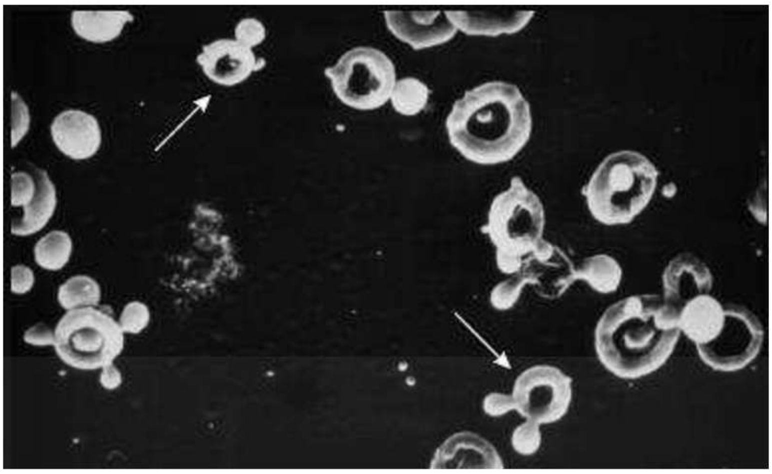

Fig: 3

URINE ANALYSIS

- Appearance
- Specific gravity
- Chemical tests (Dipstick)
  - pH
  - Protein
  - Glucose
  - Ketones
  - Blood
  - Urobilinogen
  - Bilirubin
  - Nitrites
  - Leukocyte esterase
  - Microscopic examination (formed element)

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Crystals	Urate, calcium phosphate, oxalate or carbonate, triple phosphate, cysteine, drugs
Cells	Leukocytes, erythrocytes, renal tubular cells, oval fat bodies, transitional epithelium, squamous cell
Casts	Hyaline, granular, red blood cell (RBC), white blood cell (WBC), tubular cell, degenerating cellular, broad, waxy, lipid-laden

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Infecting organism	Bacteria, yeast, trichomonas, nematodes
Miscellaneous	Spermatozoa, mucous threads, fiber, starch, hair and other contaminants

- Urine analysis
  - Physical
  - Chemical
  - Microscopy

Dipsticks Fig: 1

Fig: 2

- Based on color change, we will compare
  - Trace
  - 1+
  - 2+
  - 3+

- 4+

Collection of urine sample

- Spontaneous voiding
- Catheterized patient → Do not collect form uro bag
- Suprapubic aspiration
  - Morning sample → mid-stream of 2nd urination
  - 24-hour sample
  - Random sample
- Ideally within 2-4 hours of sample collection, urine should be examined
  - If not possible, refrigerate @ 4-8°c

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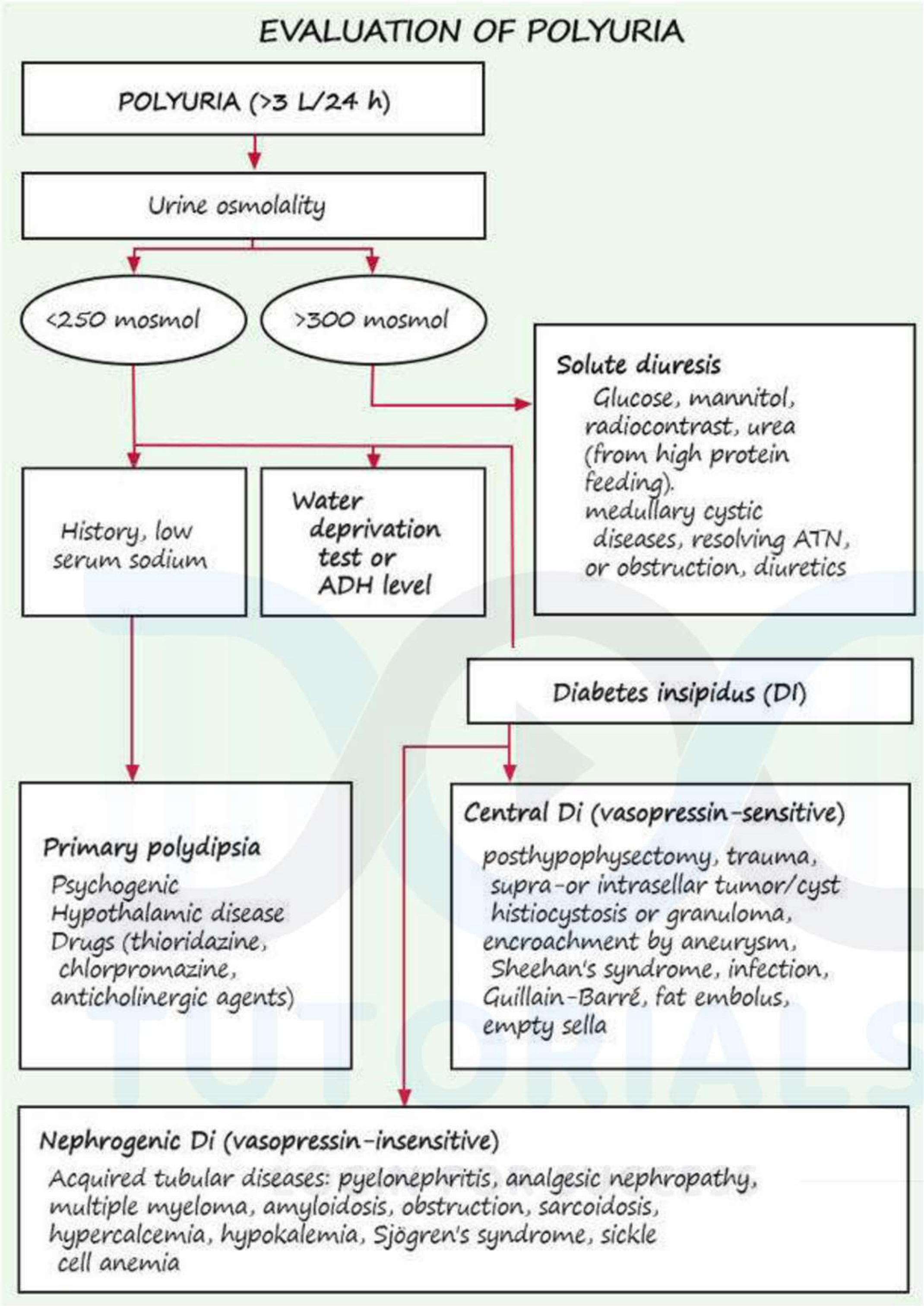

- Polyuria > 3L/day
- Oliguria < 400ml/day
- Anuria < 100ml/day

Color of urine 00:20:40

Fig: 3

Fig: 4

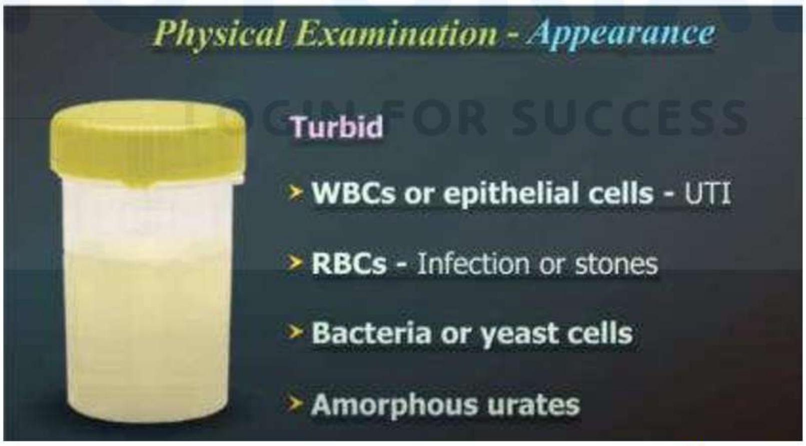

Fig: 5

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Fig: 6

Fig: 7

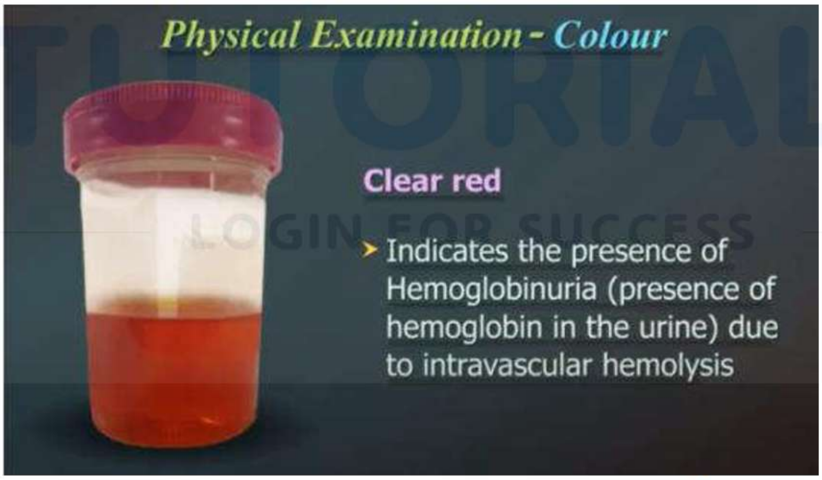

Fig: 8

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Fig: 9

Fig: 10

Urine in acute intermittent porphyria

Fig: 11

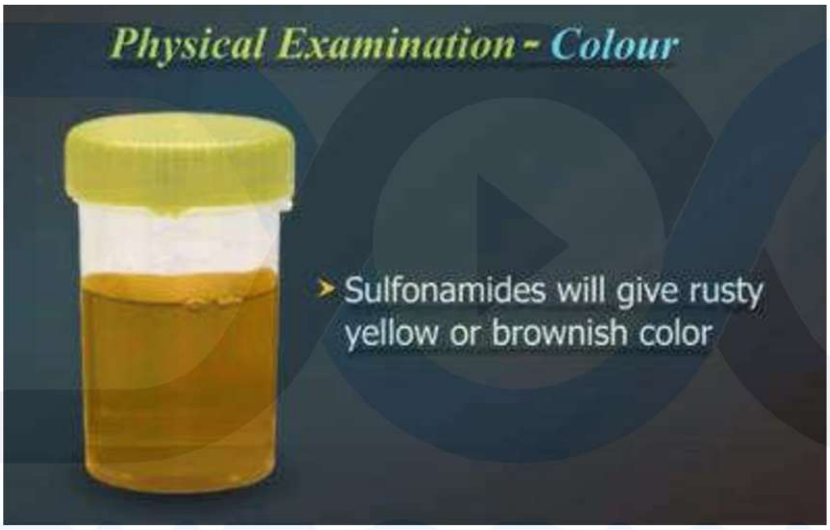

Fig: 12

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Fig: 13

- Patient on methyl dopa – brown color urine

Odor of urine 00:26:50

- Aromatic → ammoniacal

Odor	Substance or condition
Sweet or fruity	Ketones
Ammoniacal	Urea splitting bacterial infection
Maple syrup	Maple syrup urine disease
Musty or mousy	Phenylketonuria
"Sweet feet"	Isovaleric or glutamic acidemia (or) excess butyric (or) hexanoic acid
Rancid	Hypermethioninemia, tyrosinemia

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Specific gravity

- Normal = 1.003 – 1.030

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Test	Reference range	Test	Reference range
Color	Pale yellow to amber	Ketones	Negative
Specific gravity	1.003–1.030	Blood	Negative
pH	4.5–8	Leukocyte esterase	Negative
Protein	Negative	Nitrite	Negative

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Bilirubin	Negative	Urobilinogen	<0.2 -1 Ehrlich unit/dL

- Glucose -Negative

Microscopic examination of urine 00:32:24

- Done in centrifuged sample
- Look for
    - Cells
    - Casts
    - Crystals
    - Miscellaneous

i. RBC: Normal urine sample – 1 (or) 2 RBC's/hpf

ii. WBC: Normal urine sample - ≤4 WBC's/hpf
- Associated with infection – UTI
- TB (sterile pyuria)
- Fungi
- Acute interstitial nephritis
- Renal calculi

iii. Eosinophils
- Acute interstitial nephritis
- Atheroembolic disease

iv. Fat bodies

Casts

- Core of the cast is formed by Tamm Horsfall protein

i. Cellular casts → RBC cast

ii. Acellular casts → Hyaline cast and waxy cast

Cast	Main Clinical Associations
Hyaline	Normal individual, renal disease
Hyaline-granular	Normal individual; renal disease
Granular	Renal disease; acute tubular necrosis
Waxy	Renal disease with possible functional impairment
Fatty	Proteinuria; nephrotic syndrome
Erythrocyte	Glomerular hematuria; proliferative/ necrotizing GN; acute interstitial nephritis
Leukocyte	Acute interstitial nephritis; acute pyelonephritis; proliferative GN
Renal tubular epithelial cell (so-called epithelial casts)	Acute tubular necrosis; acute interstitial nephritis; proliferative GN: nephrotic syndrome
Hemoglobin	Same as for erythrocyte cast; hemoglobinuria caused by intravascular hemolysis
Myoglobin	Rhabdomyolysis
Bilirubin	Jaundice caused by increased direct bilirubin

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*atn- muddy brown granular cast

- Fat bodies – Maltese cross appearance

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A. Hyaline b.Hyaline-granular c. Granular d.waxy

Fig: 14

E. Rbc F. Hemoglobin G.wbc cast

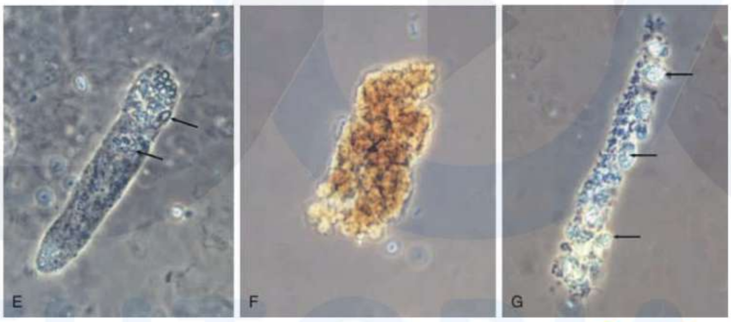

Fig: 15

H. epithelial cast I. bilirubin cast

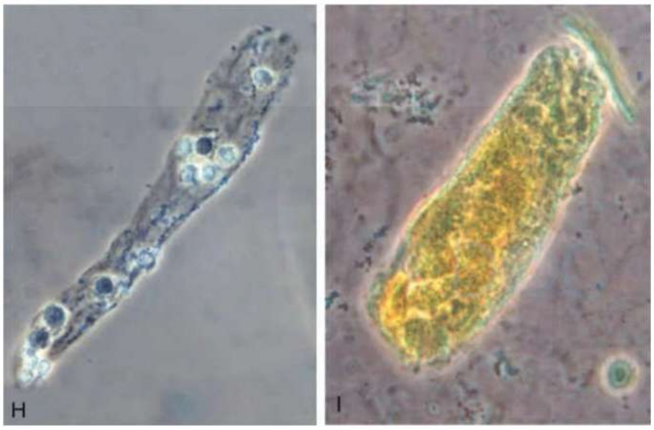

Fig: 16

Fig: 17

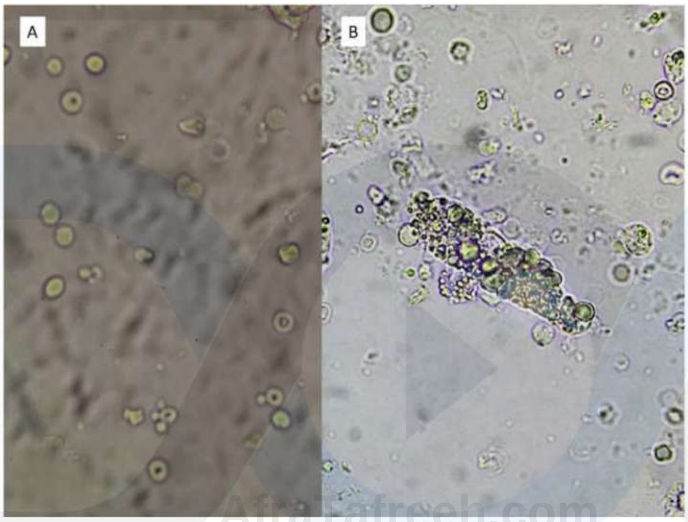

Fig: 18

Crystals 00:46:30

Crystal	Appearance
Uric acid	Usually lozenges but varying shape, yellow-tinged
Calcium oxalate	Monohydrate: ovoid or dumbbell – shaped, biconcave disks Dihydrate: bipyramidal
Calcium phosphate	Prisms, star-like particles or needles of various sizes

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Triple phosphate (struvite)	Coffin lids
Cholesterol	Transparent thin plates
Cystine	Hexagonal plates with irregular sides

- Drugs causing
  - Amoxicillin
  - Indinavir
  - Acyclovir

Uric acid crystals

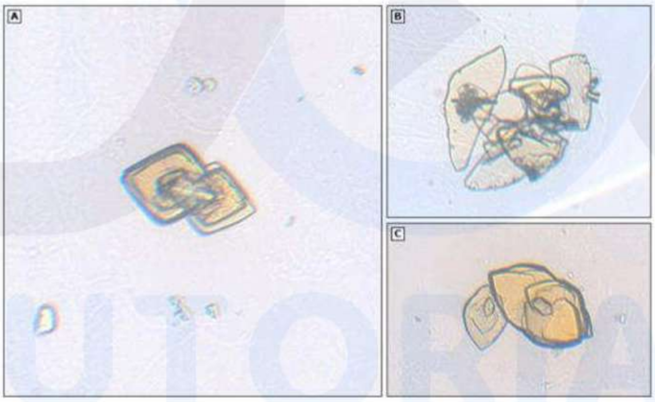

Fig: 19

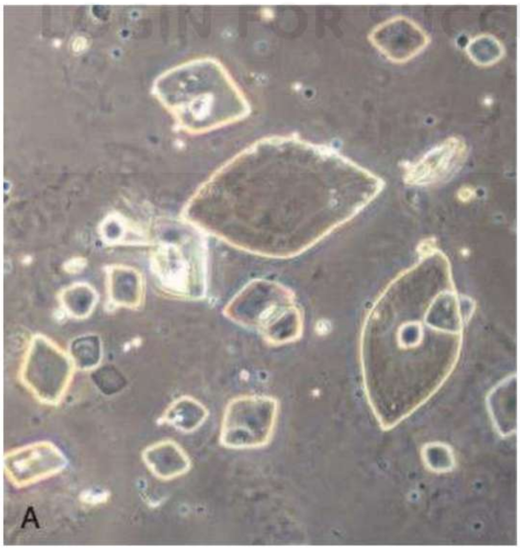

Fig: 20

B.envelopeshaped -Calcium bihydrate

C. Dumbellshaped - Monohydrate

Both b and c are calcium oxalate

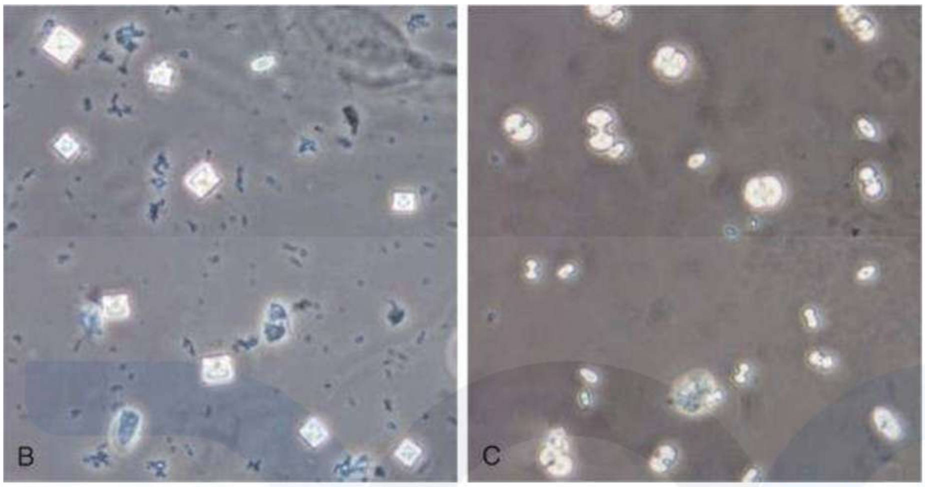

Fig: 21

Fig: 22

Fig: 23

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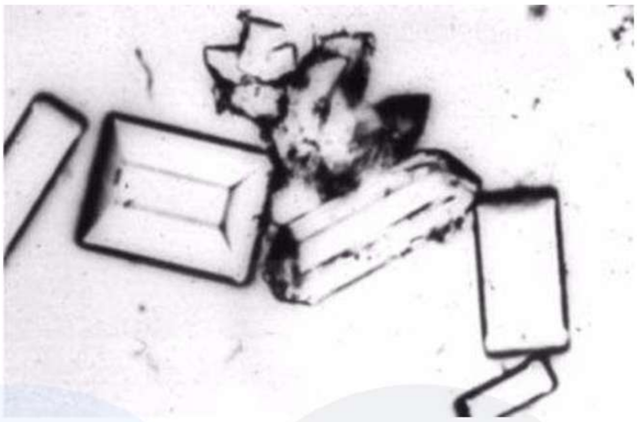
D. Star shaped crystals

↓

Calcium phosphate



E. Struvite – coffin lid Fig: 24

Fig: 25

F. Cholesterol crystals

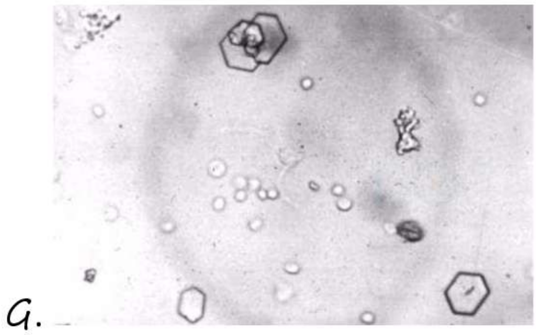


Fig: 26

G. Cystine – hexagonal shape

Fig: 27

I. Broom shaped crystals

↓

Associated with amoxicillin

J. Ciprofloxacin.   K. Indinavir

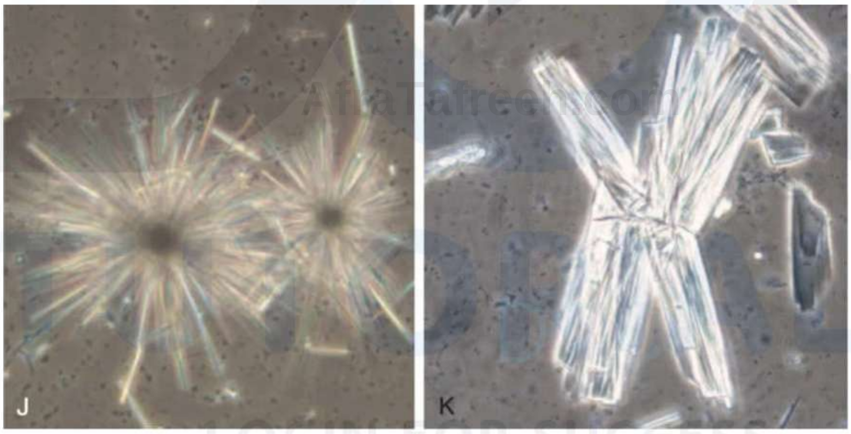


Fig: 28

Schistosoma Fig: 29

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ACUTE KIDNEY INJURY

- Previously referred to as acute renal failure
- Definition: (KDIGO – kidney diseases – improving global outcome)

AKI definition

- AKI is defined as any of the following (Not Graded):
  - Increase in SCr by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 hours; or
  - Increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
  - Urine volume <0.5 ml/kg/h for 6 hours

Stage of AKI 00:07:00

	S. creatinine	Urine output
Stage 1	>0.3 mg/dl to 1.5-1.9 times baseline	<0.5ml/kg/hour for 6-12 hours
Stage 2	To 2-2.9 times baseline	<0.5 ml/kg/hour for 12 hours
Stage 3	To ≥3time baselines (≥4mg/dl) or dialysis	<0.3ml/kg/hour for 24 hours

	S. creatinine	Urine output
Stage 1	1.5-1.9 times baseline (or) ≥0.3 mg/dl (≥26.5 μmol/l) increase	<0.5 ml/kg/h for 6-12 hours
Stage 2	2.0-2.9 times baseline	<0.5 ml/kg/h for ≥12 hours
Stage 3	3.0 times baseline (or) increase in serum creatinine to ≥4.0 mg/dl (≥353.6μmol/l) (or) Initiation of renal replacement therapy or in patients <18 years, decrease in eGFR to <35ml/min per 1.73m^2	<0.3 ml/kg/h for ≥24hours (or) Anuria for ≥12 hours

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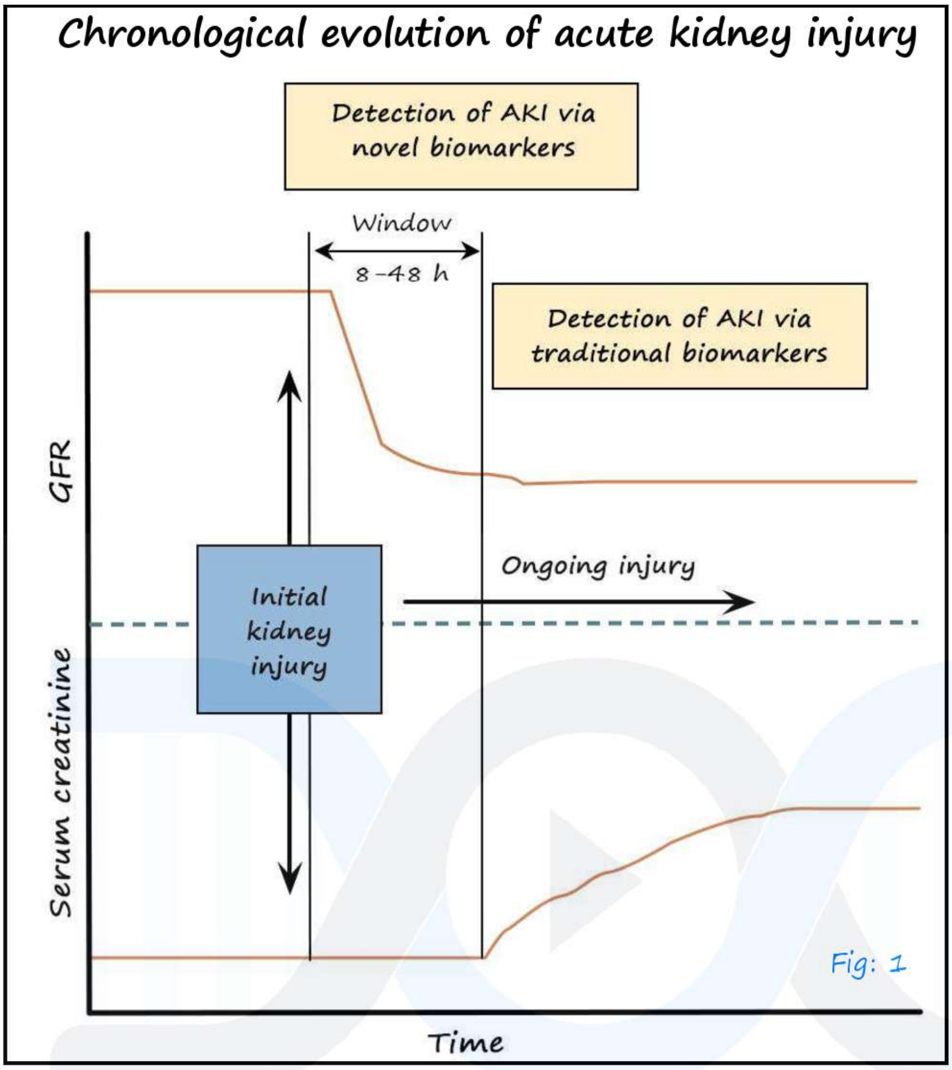


Fig: 1

Novel biomarkers for AKI 00:14:00

i. N-GAL (Neutrophil gelatinase associated lipocalcin)

ii. KIM-1 (Kidney Injury Molecule)

iii. IL-18

iv. Osteopontin

v. Cystatin C

vi. Liver type FBAP (Fatty acid binding protein)

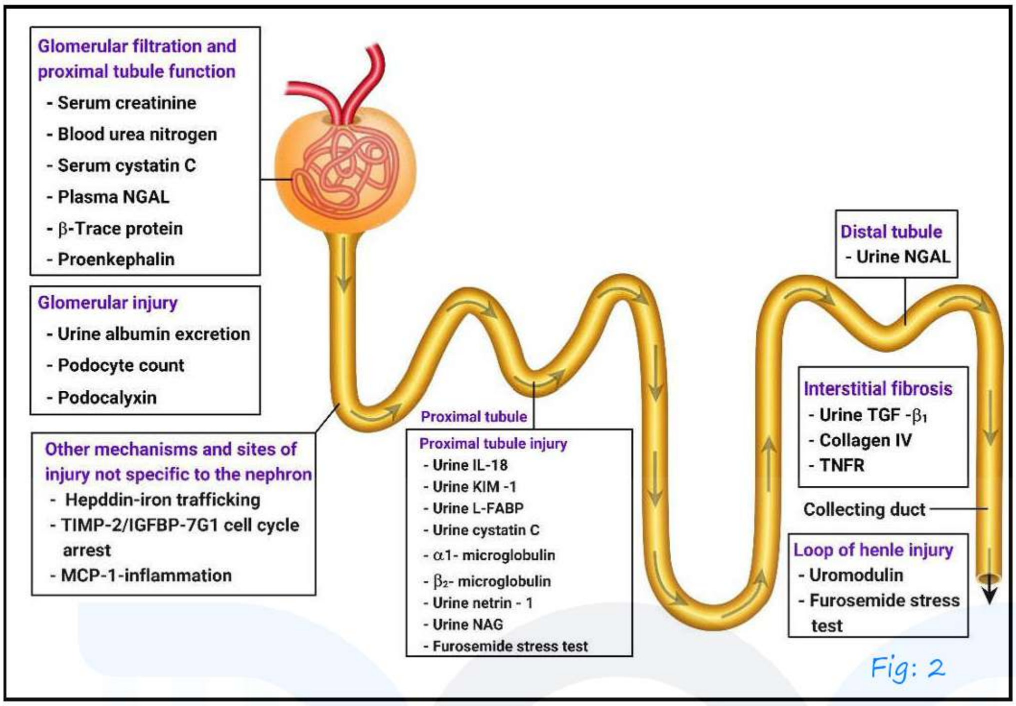
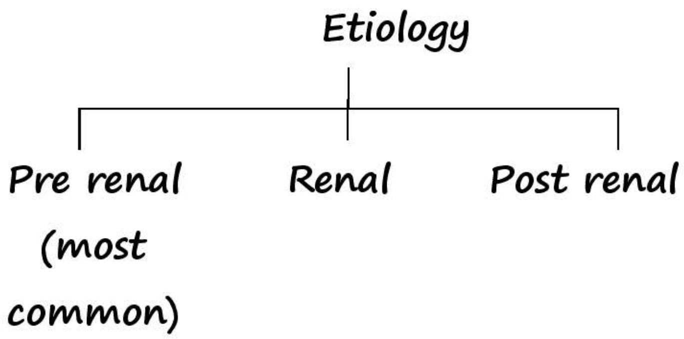


Fig: 2

Susceptibilities

- Dehydration (or) volume depletion
- Advanced age
- Female gender
- Black race
- CKD
- Chronic diseases (heart, lung, liver)
- Diabetes mellitus
- Cancer
- Anemia



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Pre renal causes

- Decrease renal perfusion because of decrease effective circulating blood volume

  i. Hypovolemia – severe diarrhoea

  ii. Cardiac failure

  iii. Liver diseases – Hepatorenal syndrome – Type 1 & 2

  iv. Drugs

  - NSAIDS
  - ACEI
  - Cyclosporine

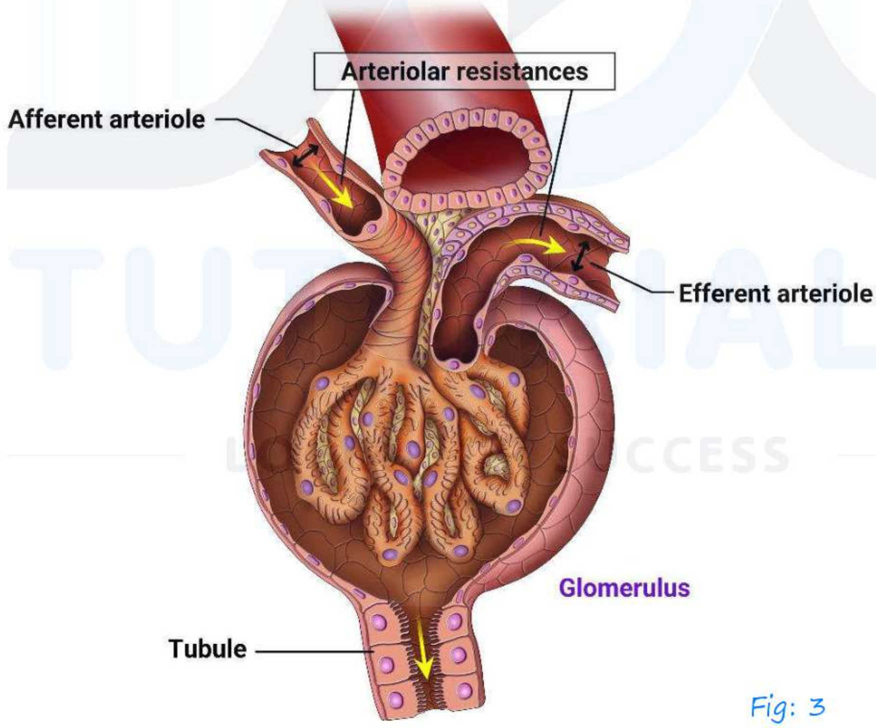

Fig: 3

- Renal autoregulation
  - Afferent arteriole dilate
  - Efferent arteriole constrict

  ] Increase intraglomerular hydrostatic pressure
  ↓
  Increase perfusion pressure

- Afferent arteriolar dilatation – prostaglandins
- Efferent arteriolar constriction – angiotension II

NSAIDS

↓

Inhibit prostaglandin synthesis

↓

Afferent arteriolar dilatation does not happen

↓

Worsens AKI

ACE inhibitors

↓

Efferent arteriolar constriction does not occur

↓

Decrease intraglomerular hydrostatic pressure

↓

Worsens AKI

Renal causes

- **Glomerular involvement** → Glomerulonephritis
- **Tubules & intersitium**
- **Vascular involvement** → TTP-HUS, Malignant HTN, Vasculitis

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Tubules & interstitum

- Acute tubular necrosis (ATN)/ Acute tubulointerstitial nephritis (ATIN)
- Causes
  - Sepsis (most common)
  - Infections
  - Nephrotoxins
    - i. Exogenous
    - ii. Endogenous

Tubular factors in the development of acute tubular necrosis

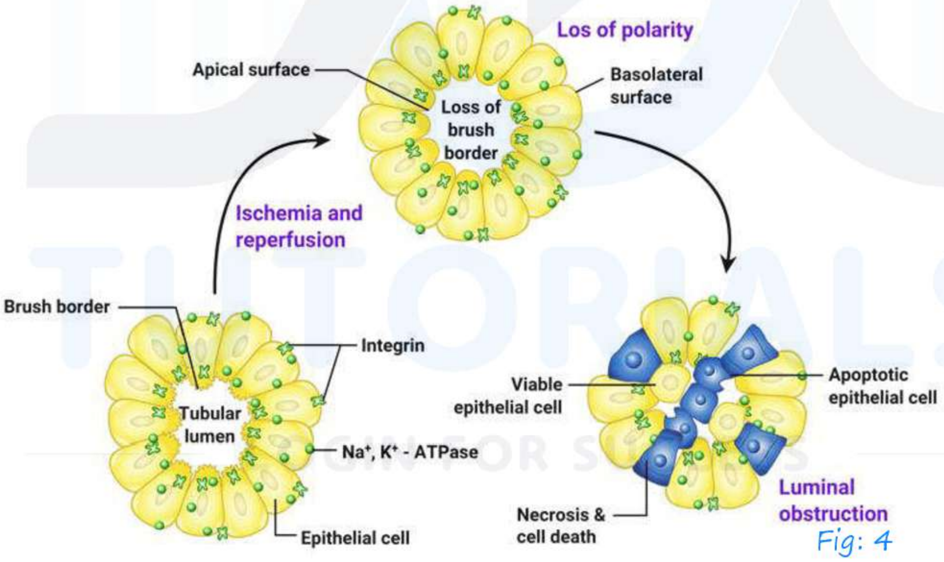

Fig: 4

Tubules and interstitium

- **Ischemia**
- **Sepsis/infection**
- **Nephrotoxins**
  - Exogenous: iodinated contrast, aminoglycosides, cisplatin, amphotericin B, PPIs, NSAIDs
  - Endogenous: Hemolysis, rhabdomyolysis, myeloma, intratubular crystals

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Postrenal

↓

Bladder outlet obstruction
Bilateral pelvoureteral obstruction (or) unilateral obstruction of a solitary functioning kidney

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Sepsis

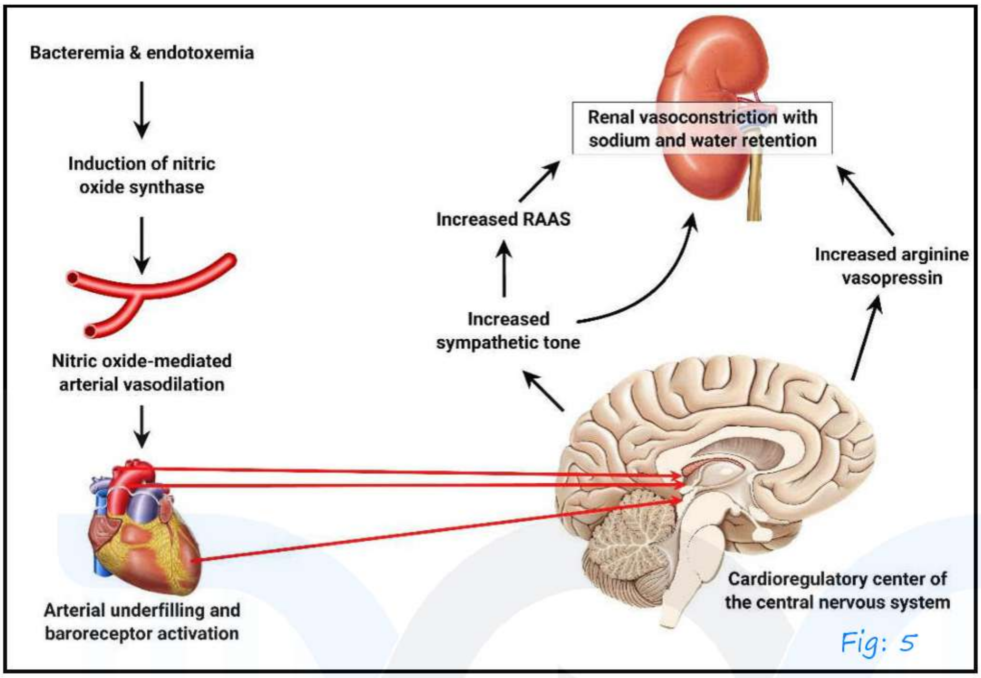

Fig: 5

Ischemia

- Kidney would receive 20% of cardiac output
- Outer medulla is very much susceptible to hypoxic injury
- S_3 segment of PCT is more susceptible to hypoxic damage

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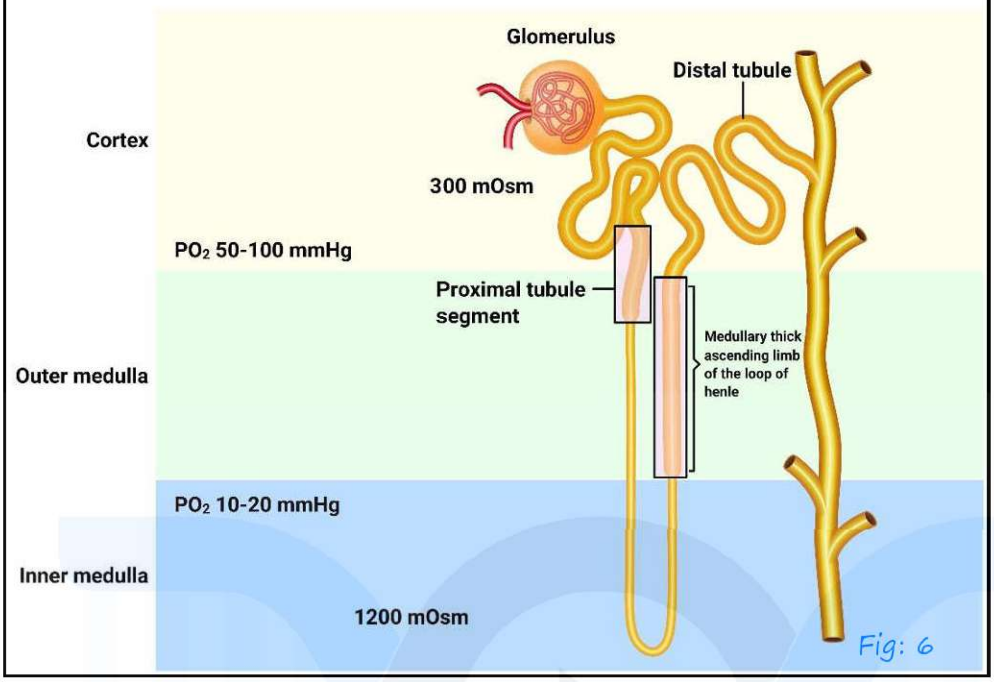

Fig: 6

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Nephrotoxins

Exogenous	Endogenous
↓	↓
Contrast media	Myoglobin
Drugs	Heme
Snake bite	Uric acid
	Myeloma light chains

Contrast Induced Nephropathy (CIN)

- Produced by Ionic high osmolar contrast media
- To prevent CIN
  - Nonionic low osmolar
  - No osmolar contrast media

  } **Preferred**

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Predisposing factors

- CKD (Diabetes, myeloma)
- Anemic
- Dehydrated
- Clinical features
  - Non-oliguric AKI
  - 24-48hours after contrast – S. Creatinine begins to increase
  - 3-5 days – S. Creatinine peaks
  - 7 days – S. Creatinine returns to normal

Prevent CIN

- Hydrate well – i.v normal saline
  - Sodium bicarbonate iv
- Oral N-acetyl cysteine (NAC)

Drugs

- Tubular necrosis
  - Aminoglycoside → Non oliguric renal failure
  - Vancomycin
  - Amphotericin B
- Interstitial nephritis
  - Hypersensitivity reaction
  - β lactam
    i. Penicillin
    ii. Cephalosporin
  - Sulfonamides

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- Quinolones
- NSAIDs

- AIN – Allergic Interstitial Nephritis
- Same patients may have
  - Fever
  - Rash
  - Arthralgia
  - Eosinophiluria

Treatment: stop the offending drug

wait for 1 week

↓

If not normalizing → Short course steroids

Crystal deposition in renal tubules

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↓

Acyclovir

Indinavir

Cancer chemotherapeutic agents

↓

Cisplatin

Carboplatin

Ifosfamide

Toxic ingestion

↓

Ethylene glycol

(Antifreeze in cars)

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- Acute tubular necrosis
- Radiocontrast
- Nephrotoxic antimicrobials
- Osmotic nephropathy
- Hydroxyethyl starch (HES)
- Intravenous immunoglobulin (IVIG containing sucrose)
- Crystal nephropathy
- Highly active anti-retroviral therapy (HAART)
- Acyclovir
- Ciprofloxacin
- Sodium phosphate purgatives
- Acute interstitial nephritis
  - Antibiotics (β-lactams, sulfa-based, quinolones)
  - Proton pump inhibitors, H_2 antagonists
  - Anti-convulsants

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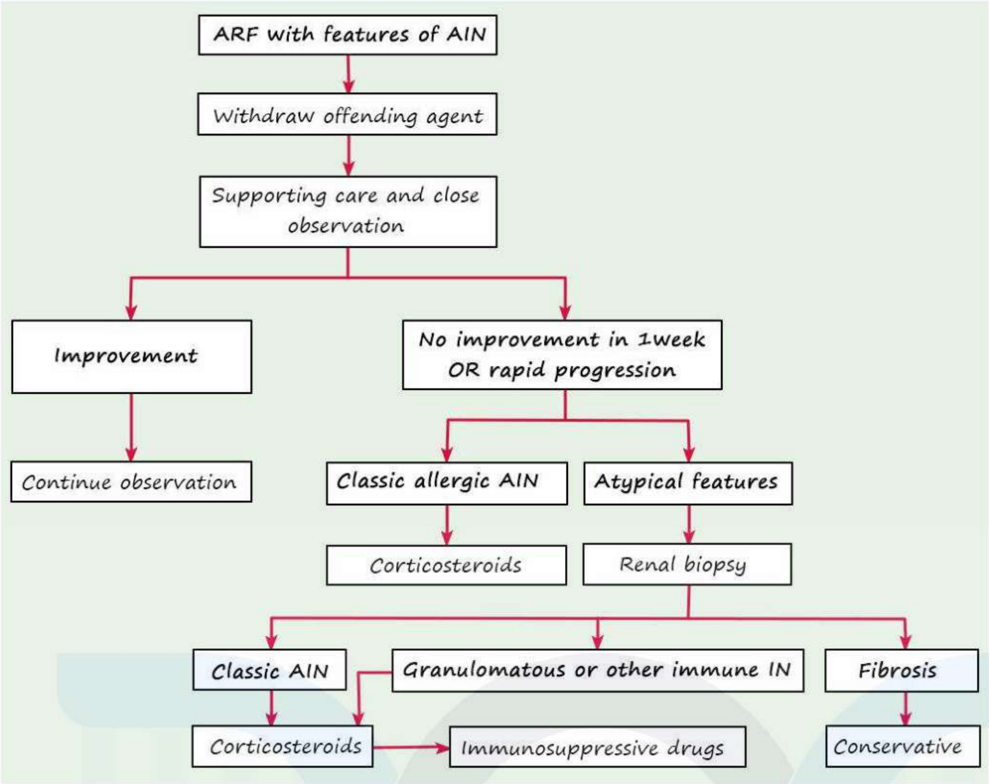

Patient-related risk factors for drug-induced nephrotoxicity
"Absolute" or "effective" intravascular volume depletion
Age older than 60 years
Diabetes
Exposure to multiple nephrotoxins
Heart failure
Sepsis
Underlying renal insufficiency (glomerular filtration rate <60ml per minute per 1.73m²)

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Endogenous toxins

- Rhabdomyolysis

Causes of Rhabdomyolysis	
Muscle injury/ ischemia	Trauma; pressure necrosis, electric shock, burns, acute vascular disease
Myofiber exhaustion	Seizures, excessive exercise, heat exhaustion
Toxins	Alcohol, cocaine, heroin, amphetamines, ecstasy, phencyclidine, snake bite
Drugs	Statins, fibrates, zidovudine, neuroleptic malignant syndrome, azathioprine, theophylline, lithium, diuretics
Electrolyte disorders	Hypophosphatemia, hypokalemia, hyperosmolar states
Infections	Viral: Influenza, HIV, coxsackievirus, Epstein-Barr virus Bacterial: Legionella, Francisella, Streptococcus pneumoniae, Salmonella, Staphylococcus aureus
Family	McArdle disease, carnitine palmitoyl transferase deficiency, malignant hyperthermia

- Hemolysis – malaria

Tumor lysis syndrome

↓

Chemotherapy aggressively for lymphoma

↓

Increase uric acid

- Light chains

Atheroembolic renal disease

- Occurs in diffuse atherosclerotic disease

Invasive vascular procedures

↓

Traumatization to plaques of atherosclerotic d/s

↓

Embolization (peripheral)

↓

Compromise renal microcirculation

↓

Renal damage

Livido reticularis Fig: 7

Blue toe syndrome Fig: 8

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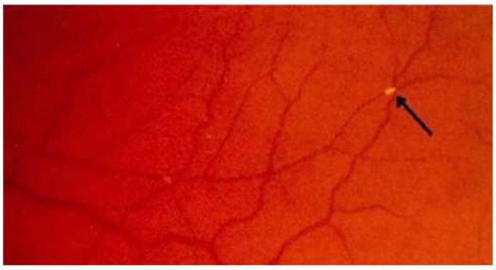

Cholesterol plaques/hollenhorst plaques Fig: 9

- Eosinophiluria ⊕

Post renal causes

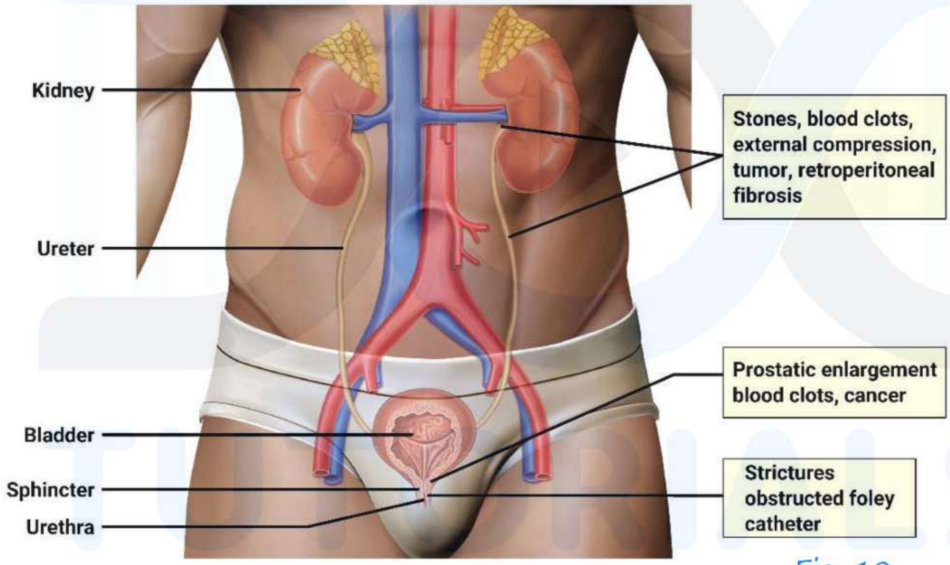

Fig: 10

LOGIN FOR SUCCESS

- BPH
- Stricture urethra
- Blocked foley's

Clinical features of AKI 01:23:10

- Asymptomatic (S.creat increase)
- Nausea, vomiting, hiccoughs → uremia
- Fluid overload

  - Puffy face
  - Acute pulmonary edema
- Decreased urine output
  - Oliguria (<400ml/day)
  - Anuria (<100ml/day)
- Uremic encephalopathy
  - Myoclonus
  - Asterixis (flapping tremor)
- Uremic pericarditis
- Myocardial depression

Investigation of AKI

- RFT
  - B. urea increased
  - S. Creatinine increased
- Electrolytes
  - Decrease Na^+ (because of volume load)
  - Hypervolemic hyponatremia
  - Hyperkalemia – ECG
  - Hyper phosphatemia
  - Hyper magnesemia
  - Hypo calcemia
- S. uric acid increase
- ABG: Metabolic acidosis
- USG abdomen/ CT abdomen → To r/o post renal causes

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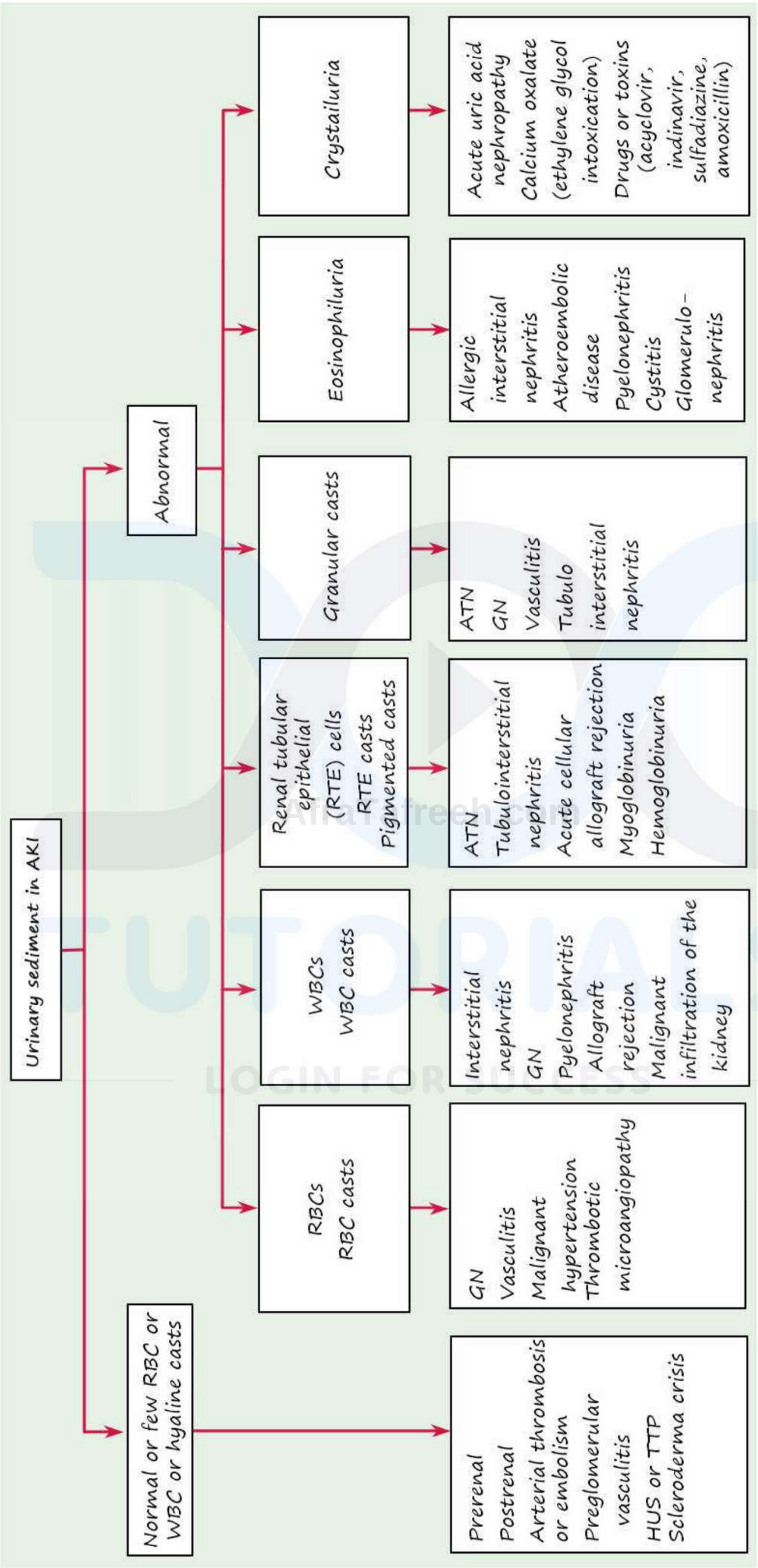
	Pre renal AKI	Intrinsic renal AKI
U. Na^+	<20 meq/L	>40 meq/L
FeNa	<1	>2
U. osmolality	>500 mosml/kg	<350
U.cr/ P.cr	>40	<20
BUN/Plasma crea	>20:1	<10:1

- FeNa – Fractional excretion of sodium

$$= \frac{(U/P)\ Na}{(U/P)\ creatinine}$$

$$= \frac{U\ Na^+}{P\ Na^+} \times \frac{P_{cr}}{U_{cr}}$$

Index	Prerenal azotemia	Oliguric acute renal failure
BUN/P_{Cr} ratio	>20:1	10-15:1
Urine sodium U_{Na}, meq/L	<20	>40
Urine osmolality, mosmol/L H_2O	>500	<350
Fractional excretion of sodium[a]	<1%	>2%
Urine/plasma creatinine U_{Cr}/P_{cr} urinalysis (casts)	>40 None or hyaline/granular	<20 Muddy brown


Urinary sediment in AKI
Normal or few RBC or WBC or hyaline casts
Prerenal
Postrenal
Arterial thrombosis or embolism
Preglomerular vasculitis
HUS or TTP
Scleroderma crisis
Abnormal
RBCs
RBC casts
GN
Vasculitis
Malignant hypertension
Thrombotic microangiopathy
WBCs
WBC casts
Interstitial nephritis
GN
Pyelonephritis
Allograft rejection
Malignant infiltration of the kidney
Renal tubular epithelial (RTE) cells
RTE casts
Pigmented casts
ATN
Tubulointerstitial nephritis
Acute cellular allograft rejection
Myoglobinuria
Hemoglobinuria
Granular casts
ATN
GN
Vasculitis
Tubulo interstitial nephritis
Eosinophiluria
Allergic interstitial nephritis
Atheroembolic disease
Pyelonephritis
Cystitis
Glomerulo-nephritis
Crystailuria
Acute uric acid nephropathy
Calcium oxalate (ethylene glycol intoxication)
Drugs or toxins (acyclovir, indinavir, sulfadiazine, amoxicillin)

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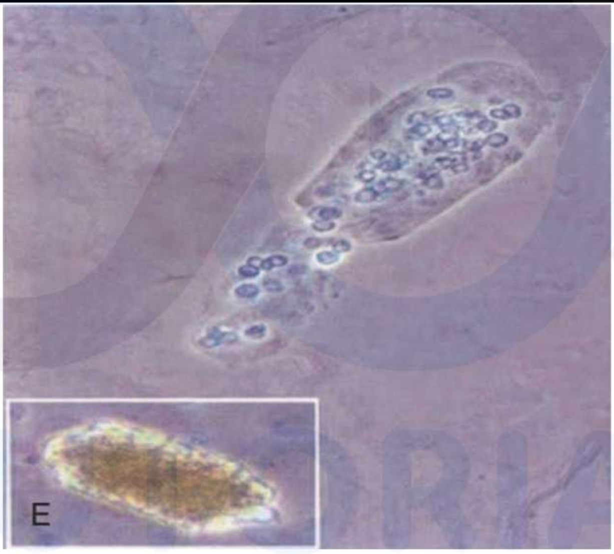
Hyaline cast Fig: 11



RBC cast Fig: 12

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Epithetical cast Fig: 13

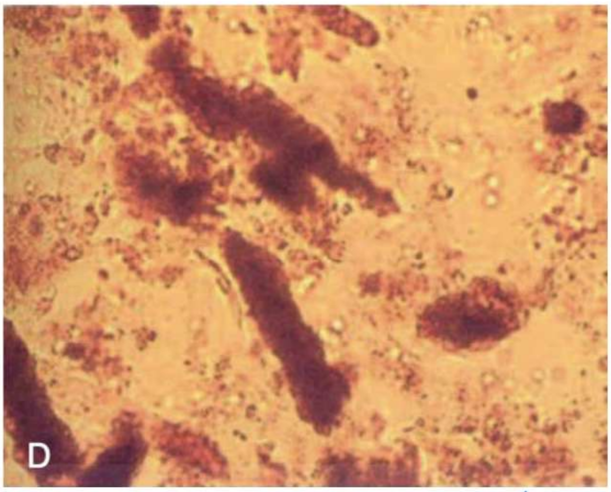

Fig: 14

Muddy brown granular cast

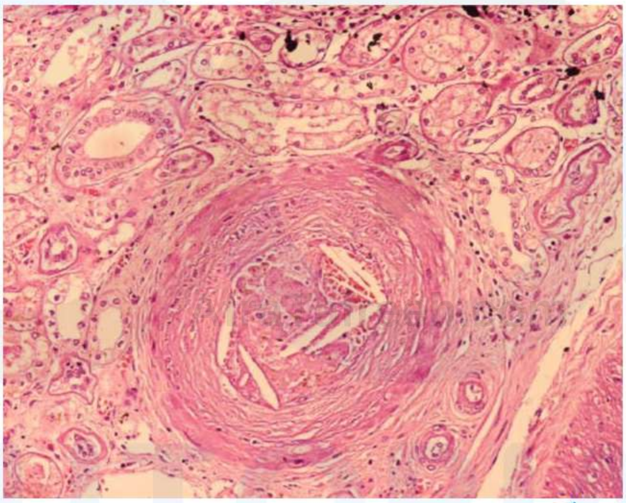

Fig: 15

Atheroembolic renal disease

Treatment of AKI 01:50:32

- Treatment underlying cause
- Fluid balance → Intake

Urine output + Insensible losses

↓

Stool, sweat, water vapour

(around 500ml)

- AKI due to dehydration → Adequate hydration
- Electrolytes → Hyponatremia

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- Restrict fluid intake
- Avoid hypotonic fluids
- If drowsy → hypertonic saline

- Hyperkalemia
  - Calcium gluconate – membrane stabilizing action
  - Insulin – redistribution of K^+
  - Salbutamol
  - Potassium binding resins
- Hyperphosphatemia
  - Dietary phosphate restriction
  - Sevelamer
- Hypocalcemia
  - Calcium supplements
- Uric acid
- Metabolic acidosis:
  - When pH <7.2 → sodabicarbonate i.v
- Hemodialysis

  i. If AKI is due to tumor lysis syndrome
  - IV fluids
  - Frusemide infusion
  - Allopurinol
  - Rasburicase

  ii. If AKI is due to rhabdomyolysis
  - IV fluids
  - Forced alkaline diuresis

INTRODUCTION AND BASICS OF CKD

CKD 00:01:00

- KDIGO Definition: - Progressive affection of kidney structure or function. > 3 months

Criteria for CKD (either of the following present for > 3 monts)	
Markers of kidney damge (one or more)	- Albuminuria (AER ≥ 30 mg/24 hours; ACR ≥ 30 mg/g [≥ 30 mg/mmol] - Urine sediment abnormalities - Electrolyte and other abnormalities due to tubular disorders - Abnormalities detected by histology - Structural abnormalities detected by imaging - History of kidney transplantation
Decreased GFR	- GFR < 60 ml/min/1.73 m^2 (GFR categories G3a-G5)

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- Progressive reduction in nephron number

  GFR? – GFR of single nephron x total no. of nephrons

- Normal GFR = 120ml/min/1.73m^2 (3rd decade)

- Grading CKD
  - GFR
  - Urinary albumin excretion

Estimation of GFR

- Inulin clearance
- Creatinine clearance
- eGFR – estimated GFR

  ↓

  Formulas to calculate eGFR
  - CKD – EPI formula (most fav)
  - MDRD formula
  - Cockroft gault formula

Recommended equations for estimation of glomerular filtration rate (GFR) using serum creatinine concentration (S_{CR}), Age, Sex, Race and Body Weight
1. Equation from the modification of diet in renal disease study

- Estimated GFR (mL/min per 1.73 m^2) $= 1.86 \times (S_{cr})^{-1.154} \times (age)^{-0.203}$ - Multiply by 0.742 for women - Multiply by 1.21 for African ancestry
2. CKD – EPI Equation - $GFR = 141 \times mins (S_{cr}/K, 1)^{\alpha} \times max (S_{cr}/K, 1)^{-1.209} \times 0.993^{Age}$ - Multiply by 1.018 for women - Multiply by 1.159 for African ancestry - Where S_{α} is serum creatinine in mg/dL, K is 0.7 for females and 0.9 for males, α is – 0.329 for females and – 0.411 for males, min indicated the minimum of S_{CR}/K or 1, and max indicated the maximum of S_{CR}/K or 1

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Grading based on GFR

- G_1 - ≥ 90ml/min
- G_2 - 60 - 89 ml/min
- G_3 - 30 – 59 ml/min
  - 3a → 45-59
  - 3b → 30-44
- G_4 – 15 – 29 ml/min
- G_5 - ≤ 15ml/min

  ESRD – End stage renal disease

  Features of uremia

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Based on urinary albumin excretion

- A_1 – ACR < 30mg/g
- A_2 – < 30- 300mg/g
- A_3 – < 300mg/g

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				Persistent albuminuria categories description and range		
				A1	A2	A3
				Normal to miidly increased	Miidly decreased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3 -30mg/mmol	>300 mg/g >30mg/mmol
GFR categories(mvmin\1.73m2) description and range	G1	Normal or high	≥90			
	G2	Miidly decreased	60-89			
	G3A	Miidly to moderately decreased	45-59			
	G3B	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Fig: 1

Chronic Kidney Disease Classification According to Glomerular Filtration Rate and Albuminuria

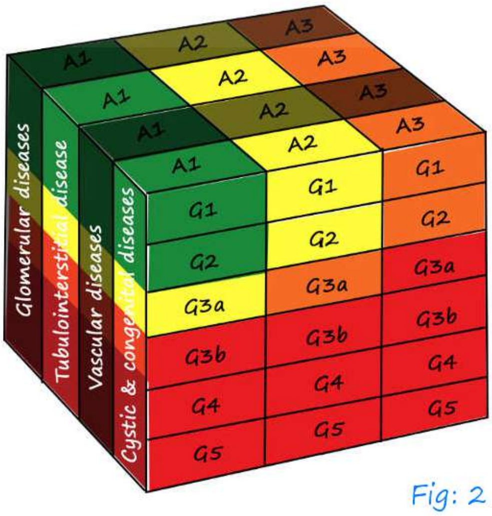

Fig: 2

GFR categories (ml/min/1.73 m²) description and range		
G1	Normal or high	≥ 90
G2	Mildly decreased	60 – 89
G3a	Mildly to moderately decreased	45 – 59
G3b	Moderately to severely decreased	30 – 44
G4	Severely decreased	15 – 29
G5	Kidney failure	< 15

Persistent albuminuria categories description and range		
A1	A2	A3
Normal to mildly increased	Moderately increased	Severely increased
<30 mg/g <3 mg/mmol	30 – 300 mg/g 3 – 30 mg/mmol	> 300 mg/g > 30 mg/mmol

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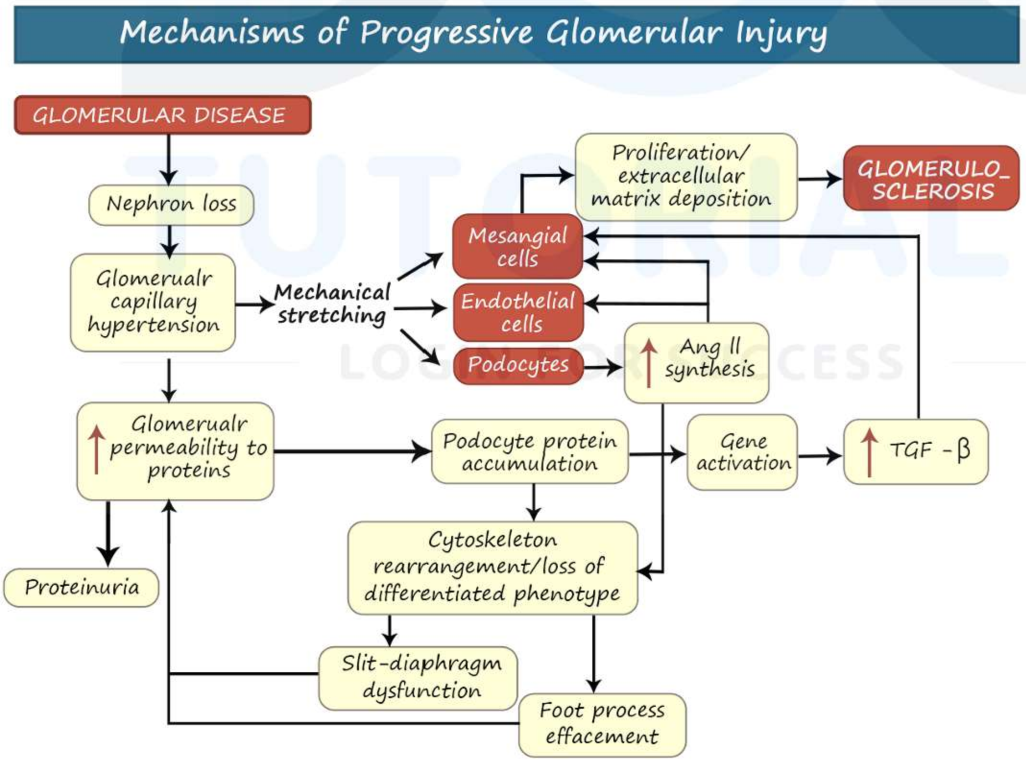
Classification of CKD based on presence or absence of systemic disease and location within the kidney	
Presence of systemic disease affecting the kidney	Primary kidney diseases
Glomerular diseases	
Tubulointerstitial diseases	
Vascular diseases	
Cystic and congenital disease	

Pathology of CKD 00:29:30



Etiology 00:31:00

- Most common cause – Diabetic kidney disease
- Chronic glomerulonephritis
- Hypotensive CKD
- Chronic tubulointerstitial diseases
- ADPKD → most common genetic cause

There will be compensatory hypertrophy and hyperfiltration → GFR normal or increase

↓

Activation of RAAS

↓

Intraglomerular HTN

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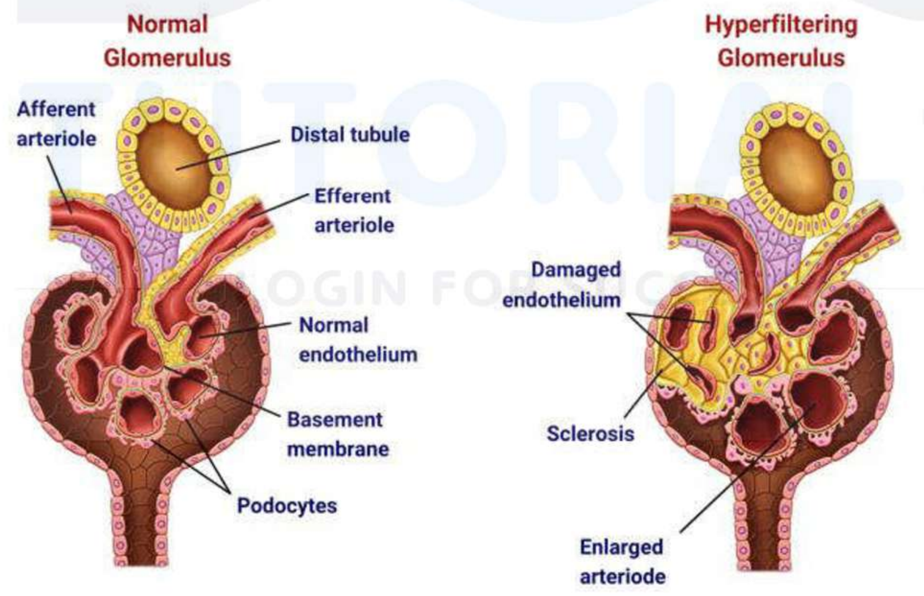

Fig: 3

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OVERVIEW OF CLINICAL MANIFESTATION

- Sometimes totally asymptomatic
- Some of the features can be explained by uremia

Fluid & electrolyte balance 00:03:55

- Fluid overload
- Pulmonary edema
- Salt retention in the body
- Hyperkalemia
- Hyperphosphatemia
- Hyponatremia
  i. Late onset
  ii. Not very common
- Metabolic acidosis

- CVS involvement
- Hematological abnormalities
- Bone and mineral abnormalities
- Neurological abnormalities
- GI abnormalities
- Dermatological manifestations
- Endocrine & metabolic

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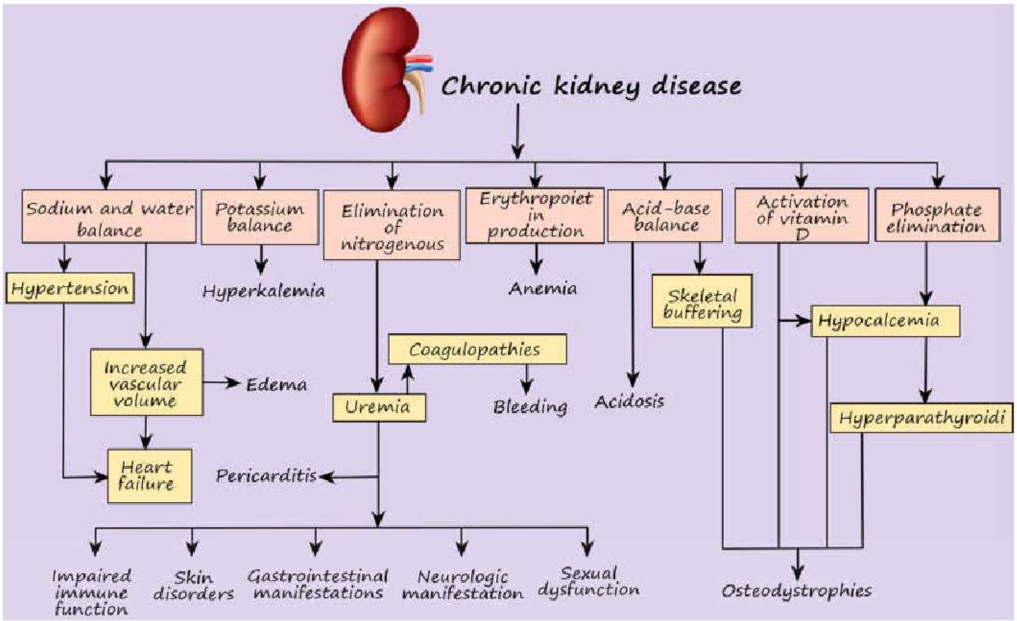

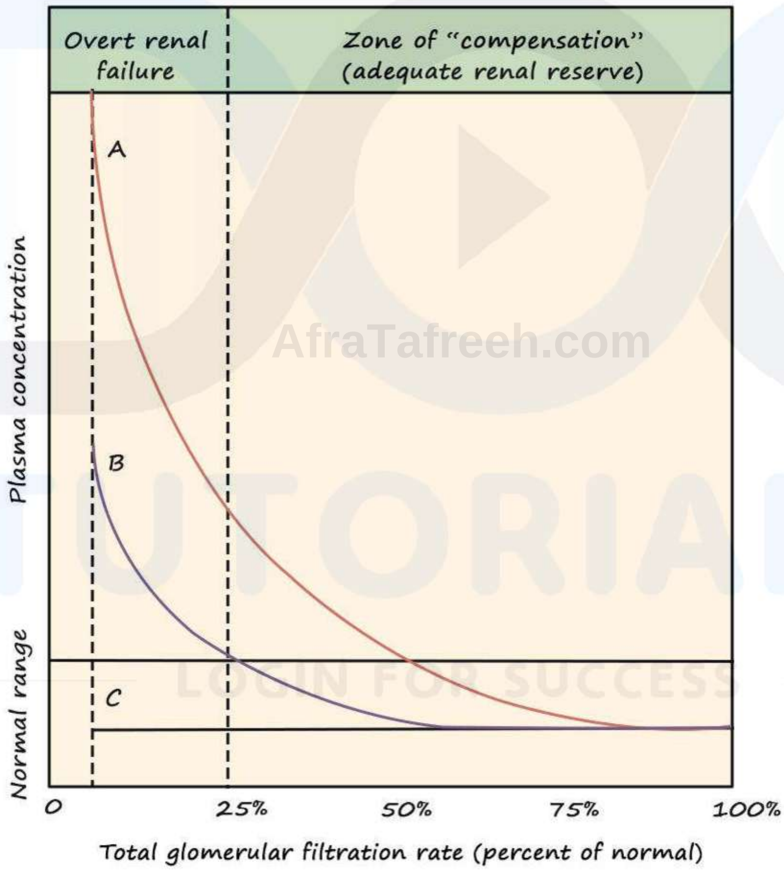

A- CREATININE

B- PHOSPHATE

C- SODIUM

- When GFR is slightly reduced, there might be elevation of concentration of serum creatinine

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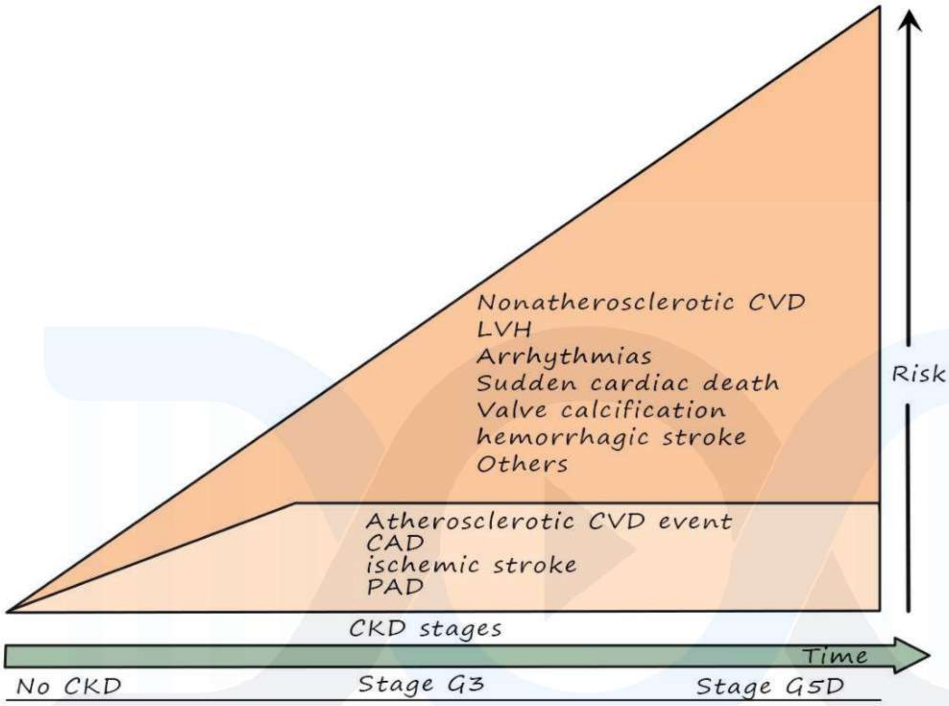
CARDIOVASCULAR MANIFESTATION OF CKD

- Most common cause of mortality in CKD



- Accelerated atherosclerosis ⊕

  ↓

  - CAD
  - IHD
  - Increases risk of PAD

- Non atherosclerotic CVD

  ↓

  - Ventricular hypertrophy
    - Eccentric
    - Concentric
  - Arrhythmias → Atrial fibrillation
  - Sudden cardiac death

- Increases risk of vascular and valvular calcification
  - Traditional risk factors (classical)
  - CKD risk factors

Traditional risk factors

Age	Hypertension
Obesity	Diabetes mellitus
Male gender	Hyperuricemia
Tobacco use	Dyslipemia
Family history	

+

Specific risk factors

CKD

- Toxic metabolites
- Albuminuria
- Inflammation
- Oxidative stress
- Endothelial dysfunction
- Anemia
- Malnutrition

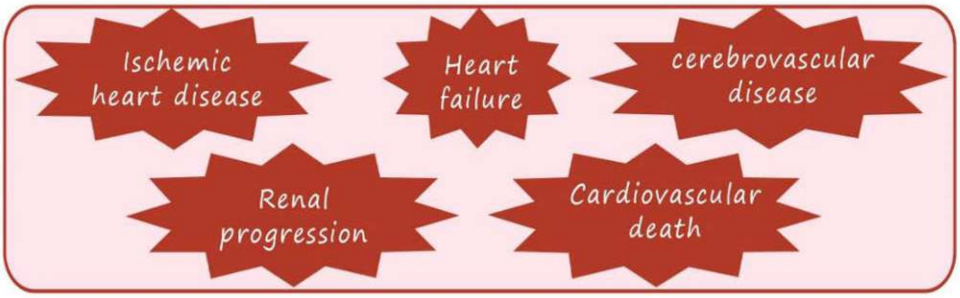
↓

Myocardium and blood vessel remodeling

↓

Cardiomyopathy — Atherosclerosis — Arterial stiffness — Calcification

↓



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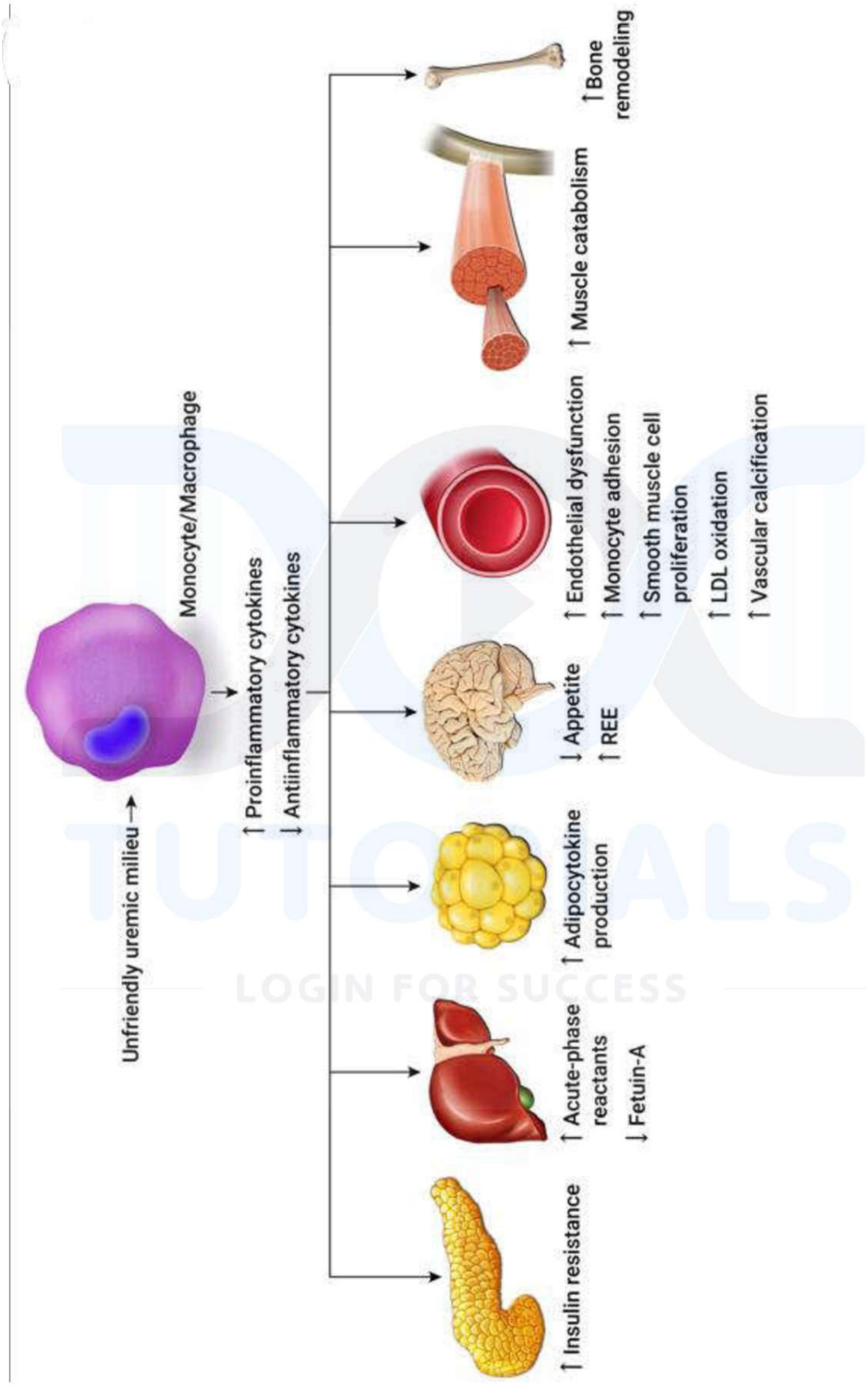
- CKD is an inflammatory state



- In CKD → ↑↑ TG

  Decreases HDL]

  T. Cholesterol] Normal

  LDL cholesterol

- CKD – On HD will have some lipid profile
- CKD on peristoneal dialysis

  ↓

  Increases TG

  Decreases HDL

  Increases Total Cholesterol

  Increase LDL

- Lipid Abnormalities in renal disease, common patterns of hyperlipidemia in different stages of renal disease, compared with the healthy population

	Cholesterol levels			
Stage of Renal Disease	Total	High-Density Lipoproteins	Low-Density Lipoproteins	Triglycerides
Nephrotic syndrome	↑↑↑	↓	↑↑	↑
Chronic kidney disease	No change	↓	No change	↑↑
Hemodialysis	No change	↓	No change	↑↑
Peritoneal dialysis	↑	↓	↑	↑

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Transplantation	↑↑	No change	↑	↑

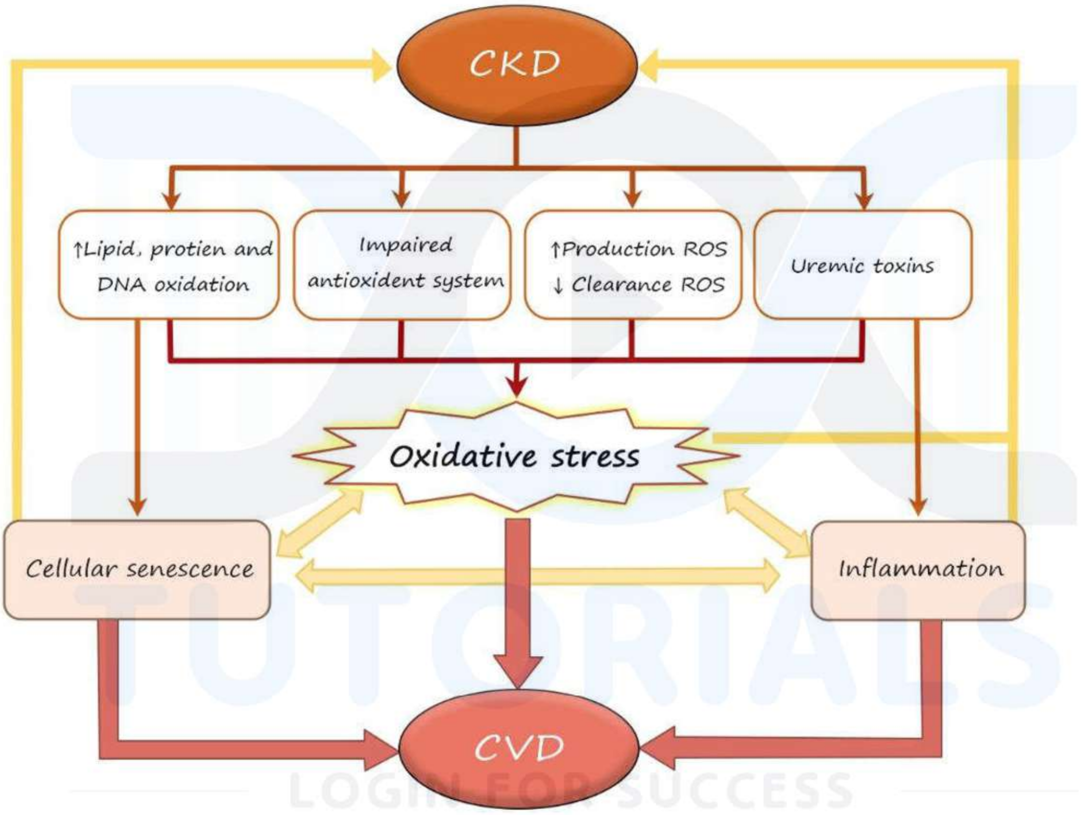
- Obese CKD patients

  ↓

  Better chance of survival

  ↓

  Reverse epidemiology & paradoxical survival risk



Uremic mileau

Other risk factors of CKD

- Hyperparathyroidism
- Hyperphosphatemia
- Increases FGF - 23

Arteries

- Increased wall thickness
- Arterial stiffness
- Endothelial dysfunction
- Arterial calcification

Heart

- Altered cardiac geometry
- Myocardial fibrosis
- Left ventricular dysfunction
- Valvular disease
- Dysrhythmia and conduction defects

Fig: 1

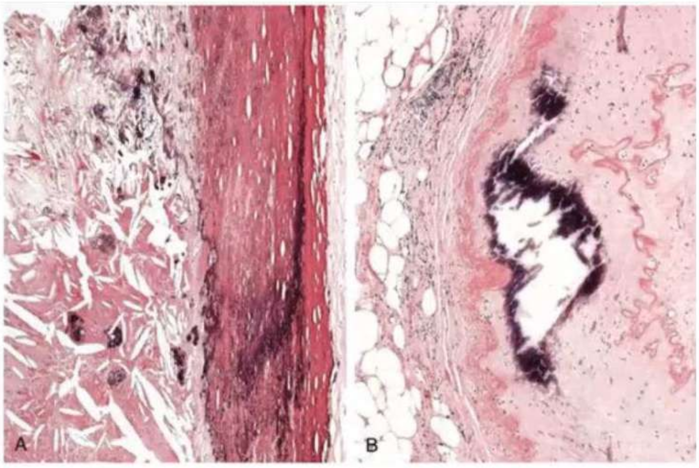


Fig: 2

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A – Tunica intima → von kossa stain – calcium

B – Tunica media

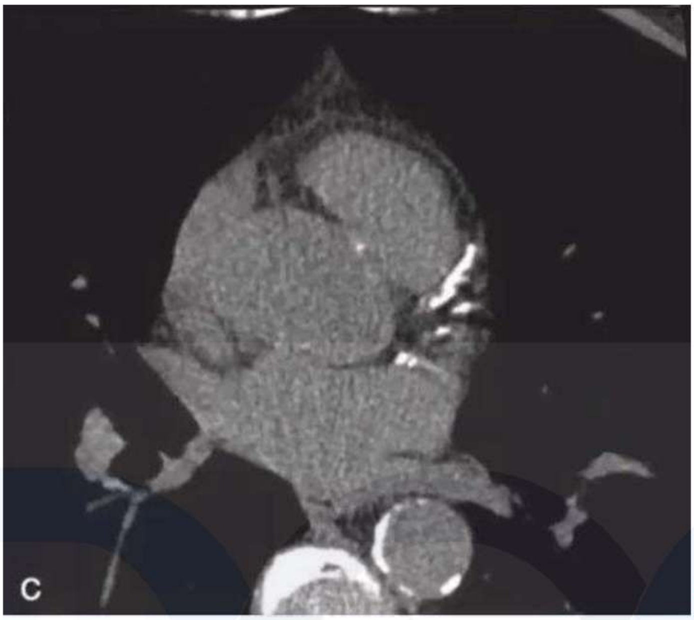

Fig: 3

CT thorax → Calcification of aorta and coronaries

Clinical manifestations 00:31:08

- HTN
- Ischemic heart disease
  - Acute myocardial infarction
  - Anginal episodes
- Features of systolic/diastolic heart failure
- Increased risk of arrhythmias – atrial fibrillation
- Pericarditis
- Peripheral vascular disease as well
- Sudden cardiac death

Investigation 00:34:52

- ECG – Ischemia changes pericarditis
- Biomarkers → Increases troponins

  ↓

  Serial estimation of troponin
- Echo – Regional wall motion abnormality

  Valve abnormality
- Dobutamine stress echo
- Coronary angiogram
- Fasting lipid levels
- Diabetic status
- Homocysteine levels
- CRP

Management 00:39:00

i. HTN

- Ambulatory BP monitoring if available (KDIGO)
- ACEI/ARB
- BP target < 130/80mmHg (20th ed. Harrison)

  March 2021 KDIGO → <120 mmHg
- In those for transplantation – BP <130/80 mmHg
- In week → moderate exercise → 150 minutes in healthy ind.
- Restrict salt intake: <5g NaCl (<2g of Na)
- Fluid intake = urine output + 500ml

ii. Judicious use of diuretics

↓

Loop diuretics

iii. Statins

↓

KDIGO guidelines

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- CKD on dialysis → stains not initiated
  → If already on statins before, can continue
- If age ≥ 50 years not on dialysis → initiate statins
- If age 18–49 years → consider statins if patient had already
- CAD
- DM
- Stroke

* Uremic pericarditis important indication for dialysis
  ↓
  Heparin free dialysis
  ↓
  Chance of cardiac tamponade
* If recurrent pericarditis ⊕ → pericardial fluid drainage
* In patients with atrial fibrillation → anticoagulation.

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HAEMATOLOGICAL MANIFESTATIONS OF CKD

- Major anaemia
- Bleeding and coagulation abnormalities

Anemia in CKD 00:01:47

- As per KDIGO guidelines
- HB < 13g% males
- < 12g1. females
- Anemia sets in when GIFR < 60ml/min - Grade 3
- Usually, normocytic normochromic anemia

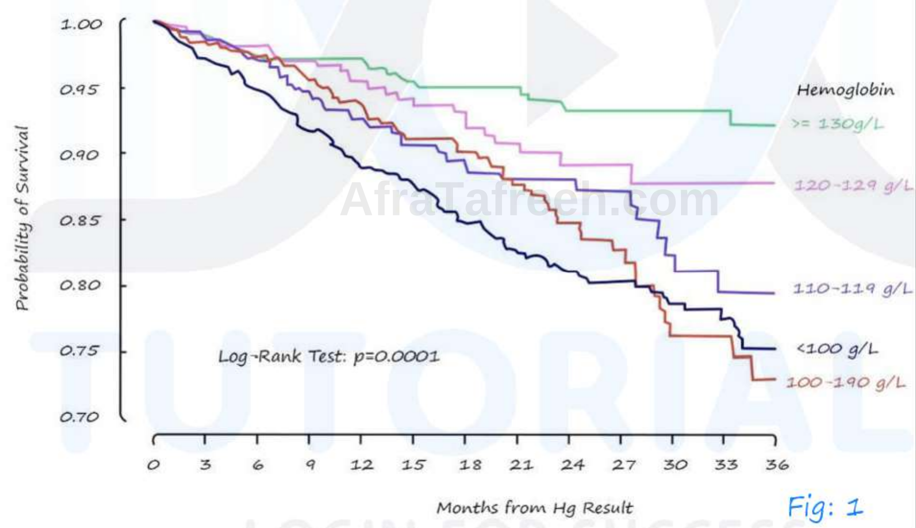

Fig: 1

- lower the Hb, bad prognosis
- Clinical features
  - fatigue
  - shortness of breath
  - Palpitations
  - Fluid overload
  - ventricular dilatation
  - ventricular hypertrophy
- Why anemia in CKD?

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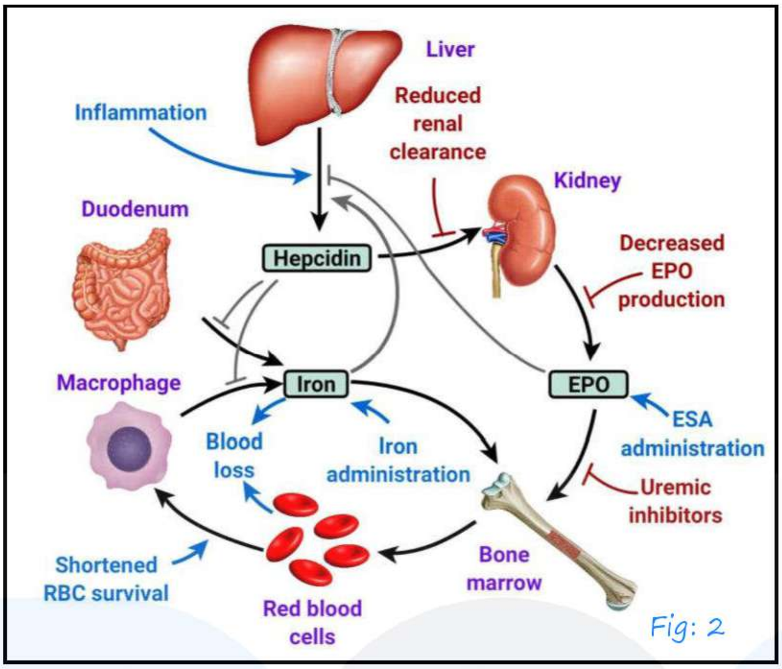

Fig: 2

- 2 most important factors to maintain Hb
  1. Iron Stores
  2. Erythropoietin→ (N) produced from interstitial fibroblasts surrounding the peritubular capillaries
- Most x cause: - Deficiency of erythropoietin (1)
- Hepcidin produced in liver is a negative iron absorption regulator
- In CKD Hepcidin accumulation

↓

Iron deficiency (2)

3. Uremia: Inhibits stages of erythropoiesis
4. Hyperparathyroidism bone marrow fibrosis
5. RBC life span shortened
6. Vit B12, folate deficiency
7. Bleeding diatheris

Causes of Anemia in CKD

- Relative deficiency of erythropoietin

- Diminished red blood cell survival
- Bleeding diathesis
- Iron deficiency due to poor dietary absorption and gastrointestinal blood loss
- Hyperparathyroidism/bone marrow fibrosis
- Chronic inflammation
- Folate or vitamin B12 deficiency
- Hemoglobinopathy
- Comorbid conditions: hypo-/hyperthyroidism, pregnancy, HIV-associated disease, autoimmune disease, immunosuppressive drugs

Treatment

- Hb target: - 10-11-5
- Iron supplements
- Erythropoiesis stimulating agents (ESA)
- Iron
- If Ferritin <500 ng/ml
  Transferrin saturation < 30%
  } KDIGO
- IV on preferred over oral
- Iron carboxymaltose

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ESA

- Check Iron Status

ESA	Dosage recommendation	Route
First generation		
Epoetin – alfa or epoetin beta	50-100IU/Kg thrice a week	(SC) or IV
Second generation		
Darbepoetin alfa	0.45mcg/kg once weekly	(SC) or IV
	0.75mcg/kg once every 2 weeks	SC
Third generation		
CERA	0.6mg/kg once every 2 weeks	SC-CKD ND IV-CKD 5D
	1.2mg/kg once every 4weeks	SC-CKD ND

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- CERA - Continuous Erythropoietin receptor activator

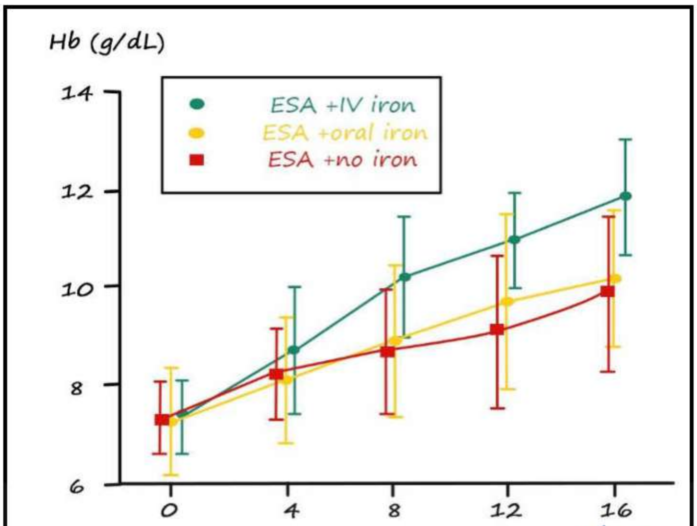

Fig: 3

- Max. benefit → ESA + iv iron

Too much of ESA

- Hypertension
- Thrombotic events
- Increased risk of stroke

HIF Stabilizers

- Hypoxia inducible factor
- Daprodusat
- Roxadusat .

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MINERAL BONE DISEASE

Mineral Bone Disorder 00:00:38

i. Bone changes

ii. Labarotory parameters

- PTH
- S. Ca^{2+}
- S. PO_4^{3-}
- FGF-23
- Calcitriol

iii. Vascular and soft tissue calcifications

- **Renal osteodystrophy:**
- Skeletal changes that occur specific to CKD

In patients of CKD

→ (m/c) high bone turnover → Osteits fibrosa cystica

→ Low bone turnover → Adynamic bone disease

- Some individuals may have combination of high bone turnover + low bone turnover
- Mixed disease

Balance of Phosphorus Metabolism

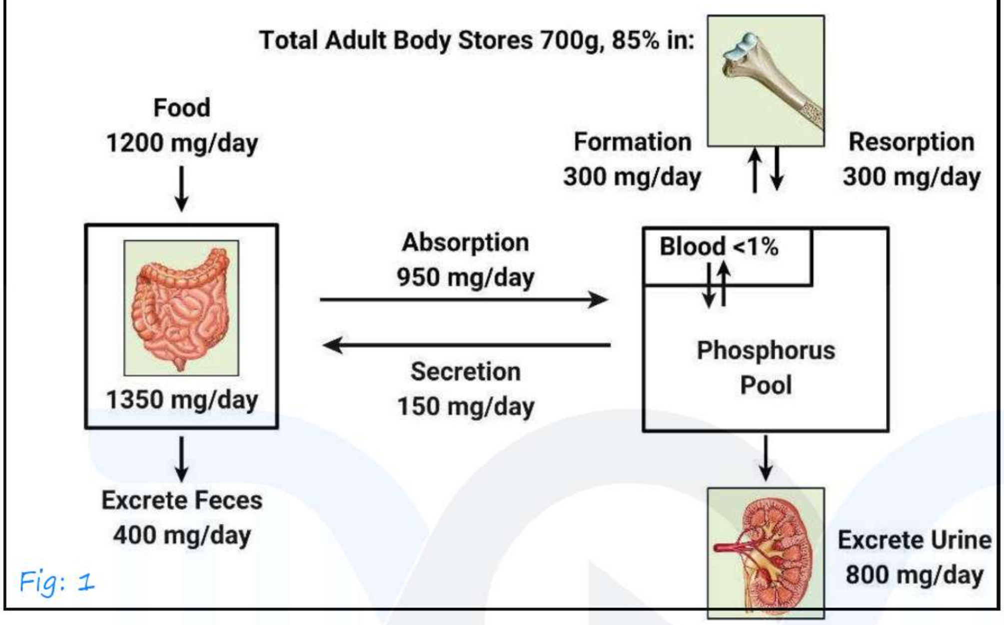

Fig: 1

Pathophysiology of Secondary Hyperparathyroidism

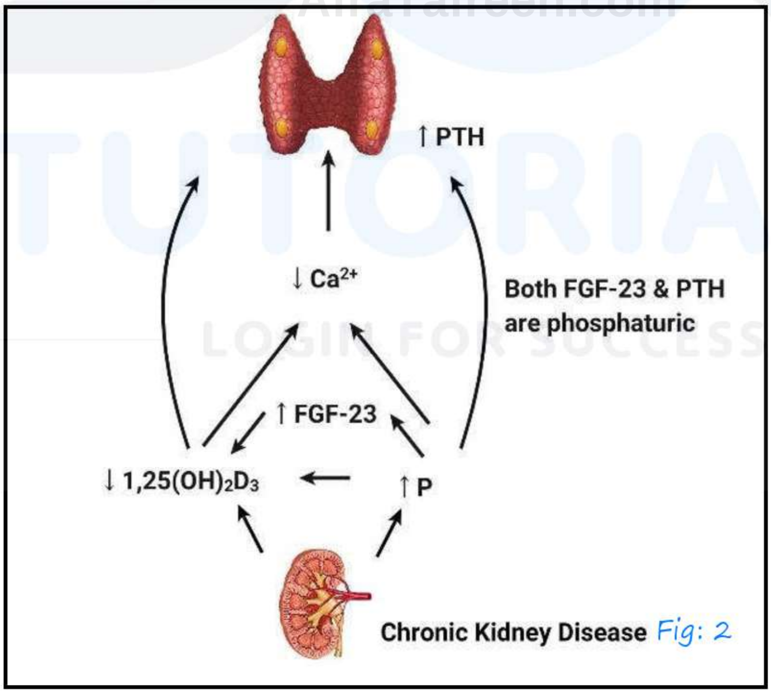

Fig: 2

- GFR < 60 ml/min

  ↓

  Interferes with excretion of body phosphorous

  ↓

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Increases phosphate levels

↓

Osteocytes secrete FGF.23 (fibroblast growth factor) (phosphaturic)

↓

Increased excretion of phosphate

↓

FGF 23 → inhibits 1 α hydroxylase

↓

Conversion of 25 hydroxy vitmin.D

↓

1,25 dihydroxy vitamin.D (calcitriol)

↓

Decreases calcitriol

↓

Hypocalcemia

↓

Secretion of PTH (2° hyperathyroidism)

- Hyperphosphatemia→ can cause calcification in blood vessels (tunica media) → stiff
- Increases PTH → Increases osteoblastic and osteoclastic activity

↓

- Increases bone mass → Woven bone
- Abnormal osteoid
- Defective mineralization

(Abnormal osteoid, Defective mineralization) →
- Increases chance of fracture
- Bone pain

Osteritis fibrosa cystica

- High bone over disease
  - Areas of bone + fibrosis + cystic lesion

- Areas of hemorrhages also

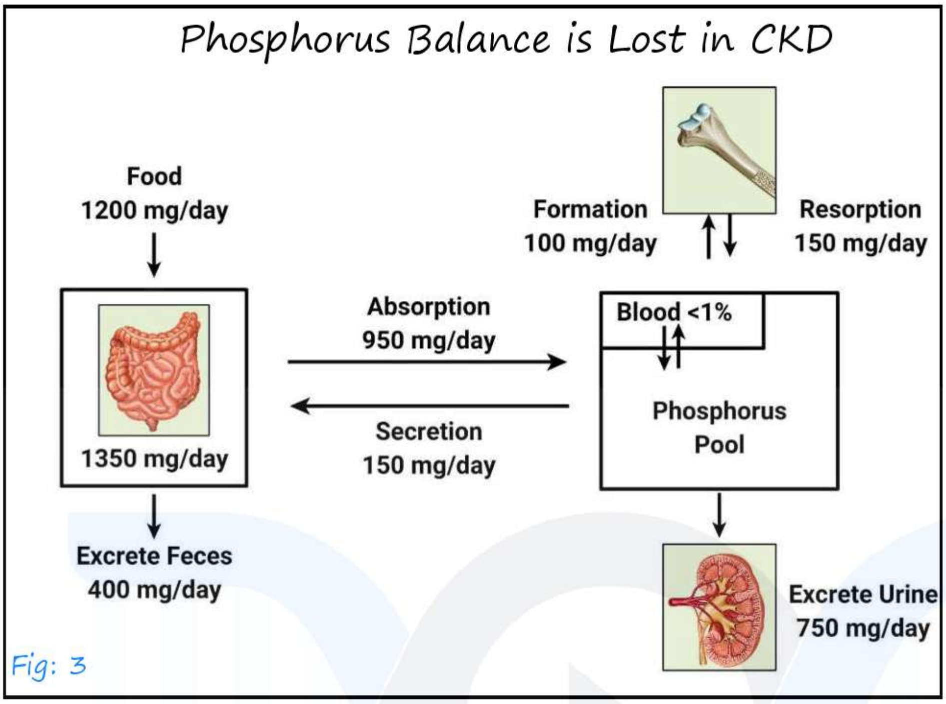

Fig: 3

Biochemical parameter	Primary hyper parathyroidism	Secondary hyper parathyroidism	Tertiary hyper parathyroidism
Calcium	Increases	Decreases	Increases
Phosphate	Decreases	Increases	Increases
iPTH	Increases	Increases	Increases

Fig: 4

osteitis fibrosa cyctica

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RIB.. Brown tumor of hyper parathyroidism

↓

Von Recklinghausen disease of bone Fig: 5

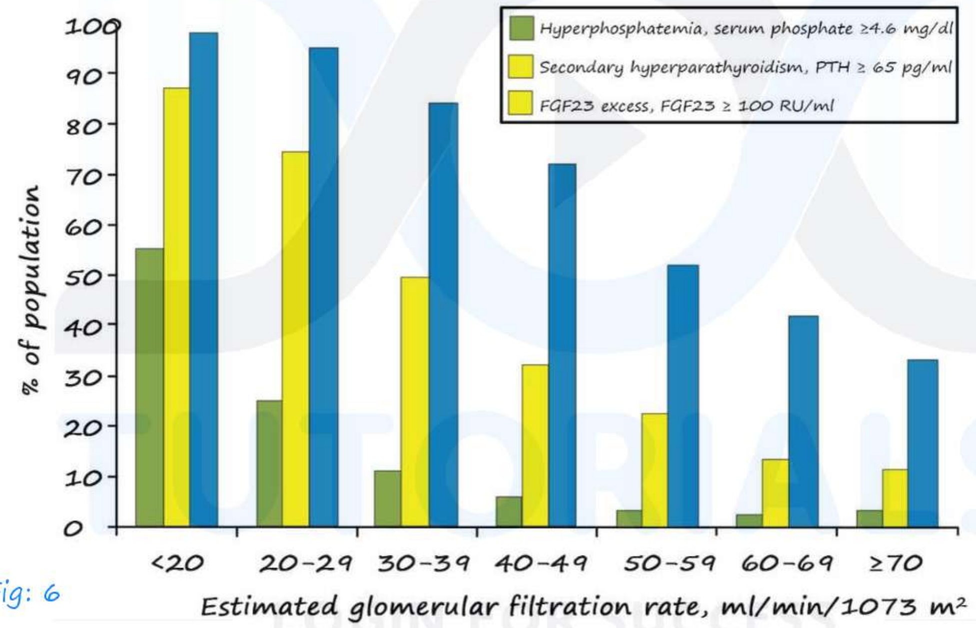

Fig: 6

Low bone turnover disease 00:38:38

- Adynamic bone disease
- In CKD → Ca^{2+} supplements, Vitamin.D3, Calcium dialysate } ↓↓↓PTH
- Decreases osteoblastic and decreases osteoclastic activity

- Mineralization of bone is normal

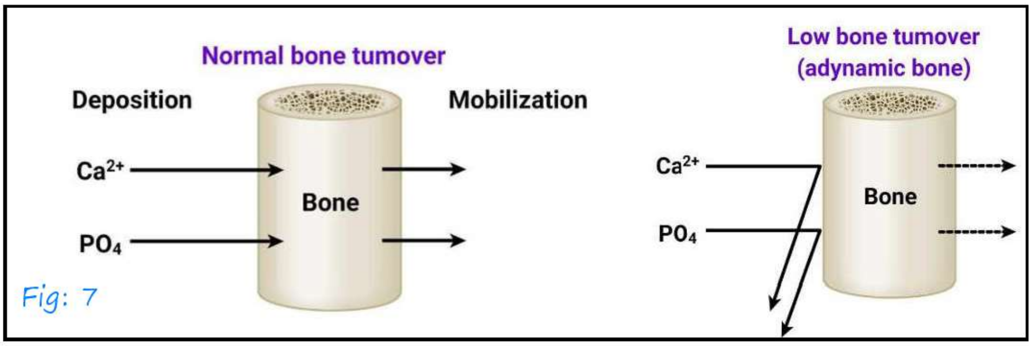

Fig: 7

- Vascular & soft tissue calcification positive

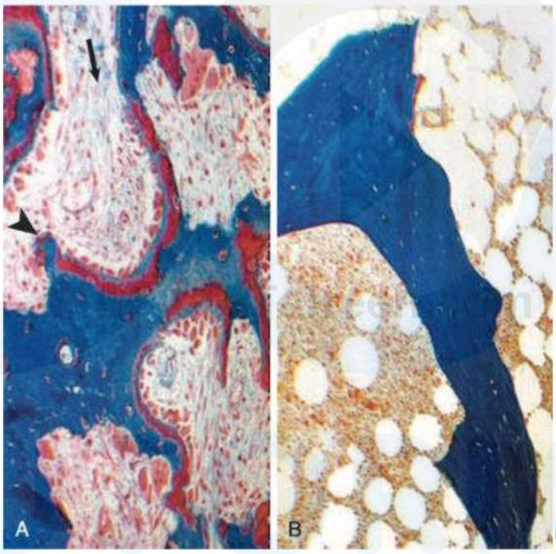

Fig: 8

- A – Osteitis fibrosa cystica
- B – Adynamic bone d/s

TUMORAL CALCINOSIS Fig: 9

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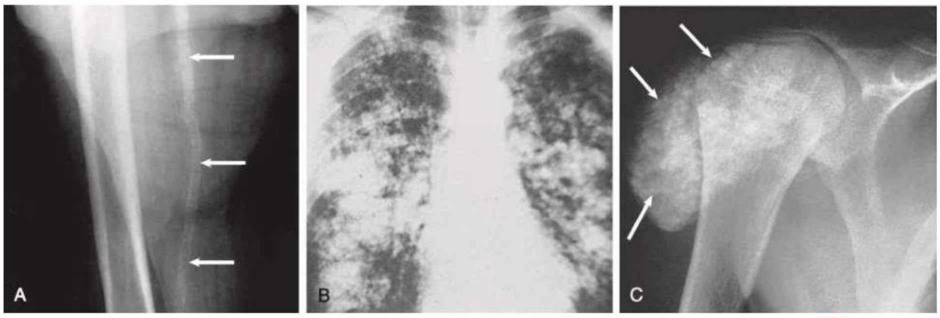

Fig: 10

- A.Vascular calcification
- B.Pulmonary calcification
- C.Periarticular calcification

- Other skeletal disorders
  i. Osteomalacia → defective mineralization
  ii. Osteoporosis

Treatment 00:47:10

- High bone turn over d/s
  a. Restrict dietary phosphates → diary products ,canned foods
  b. Phosphate binders
    - Calcium acerate
    - Calcium carbonate ↓ Increases calcium
    - Sevelamer
    - lanthanum
  c. Calcium sensing receptor agonists → cinacalcet

Indications for parathyroidectomy

- Severe hyperparathyroidism
  - With persistent hyperphosphatemia
  - Unresponsive to calcitriol and calcium
  - With hypercalcemia
  - With intolerance or unresponsiveness to calcimimetics
  - In renal transplantation candidate
  - With evidence of metastatic calcification
- Calciphylaxis with evidence of hyperparathyroidism
- Severe pruritus, only if additional evidence of hyperparathyroidism
- Low bone turnover disease (Adynamic d/s)

  i. Stop calcium and vitamin.D supplements

  ii. Calcium free dialysate

Role of PTH in Development & Progression of Renal Osteodystrophy

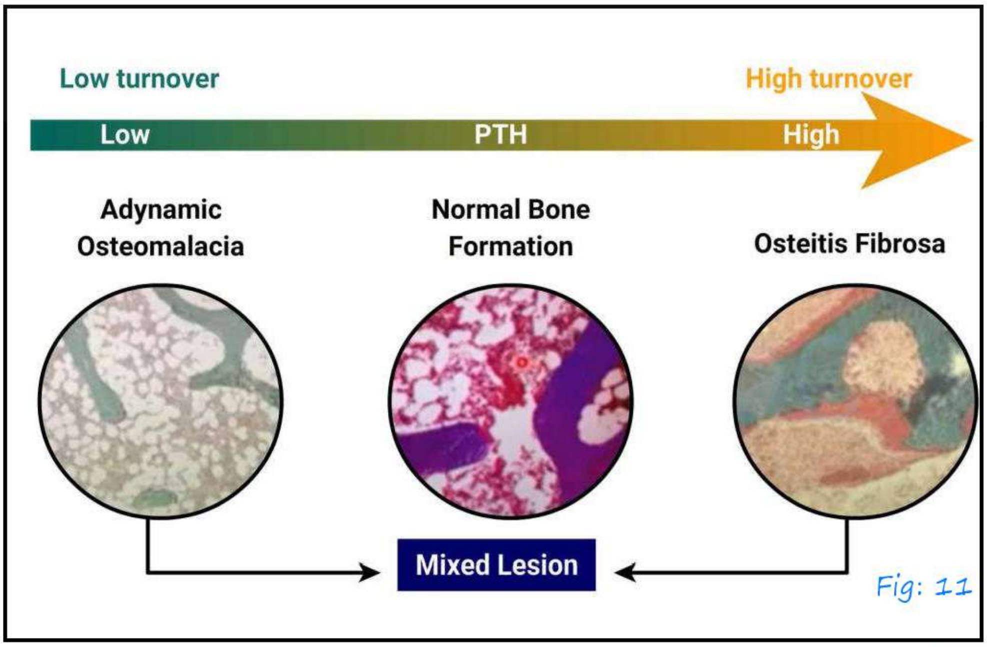

Fig: 11

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DERMATOLOGICAL MANIFESTATIONS OF CKD

Fig: 1

- Pruritis – common manifestation
  ↓
  Linear excoriations

Fig: 2

- Xerosis
  Icthyosis
  Hypopigmentation (or)
  Hyperpigmentation

Fig: 3

- Acquired perforating dermatosis

↓

There is some perforation because of which dermal contents seep through the epidermis

↓

Transepidermal perforation

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Fig: 4

- Dermal connective tissue is going access to epidermis

Fig: 5

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Calciphylaxis 00:07:36

- Seen in ESRD with secondary hyper parathyroidism
- Those who are on – Calcium containing phosphate binder
  - Warfarin

Medial calcification

Presentation

- Livedo Reticularis
- Erythernous lesion

→ Formation of eschar

Fig: 6

- Common sites
  - Breast
  - Abdomen
  - Thigh
  - Buttocks
  - Legs

Fig: 7

- Warfarin inhibits vitamin K dependent clotting factors, also inhibits matrix GLA protein (Vitamin K dependent)
- Normal function of matrix GLA protein is prevent unnecessary calcification.

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- Also known a calcific uremic arteriolopathy

Poryphria cutanea tarda Fig: 8

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Eruptive xanthomas Fig: 9

Iododerma Fig: 10

- When a CKD patient is given i.v contrast with Iodine containing agents – papulonodular lesions → Ioderma

Fig: 11

- When A-V shunt is created with chronic kidney disease.

↓

Decreased perfusion distal to A-V fistula

↓

Gangrene (Dialysis associated steal syndrome)

Nephrogenic systemic fibrosis 00:14:49

Fig: 12

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↓

Occurs in CKD patients when GFR <30ml/min

↓

Gadolonium contrast used

- Skin thick and indurated
- Contractures are formed
- Shiny skin
- This may develop even if GFR is 30-59 ml/min

Fig: 13

Cobble stone appearance of Indurated skin

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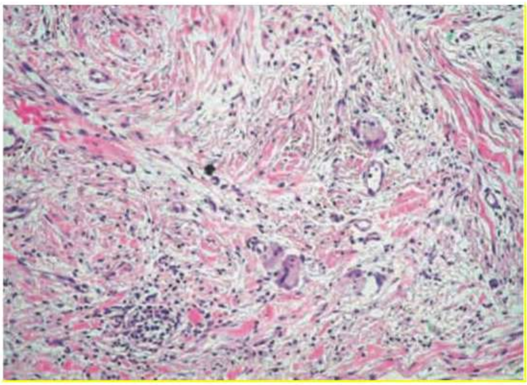

HPE image Fig: 14

Fig: 15
Lindsay's nail (half-half nail)

- Lindsay's nail (Half-half nail)

↓

Proximal portion – pale (chronic anemia)

Distal portion – dark (melanin deposition).

NEUROLOGICAL MANIFESTATIONS OF CKD

- Can affect both central nervous system and peripheral nervous system
- Impact occurs when it crosses stage 3
- Why dose CKD patient develop neurological manifestations

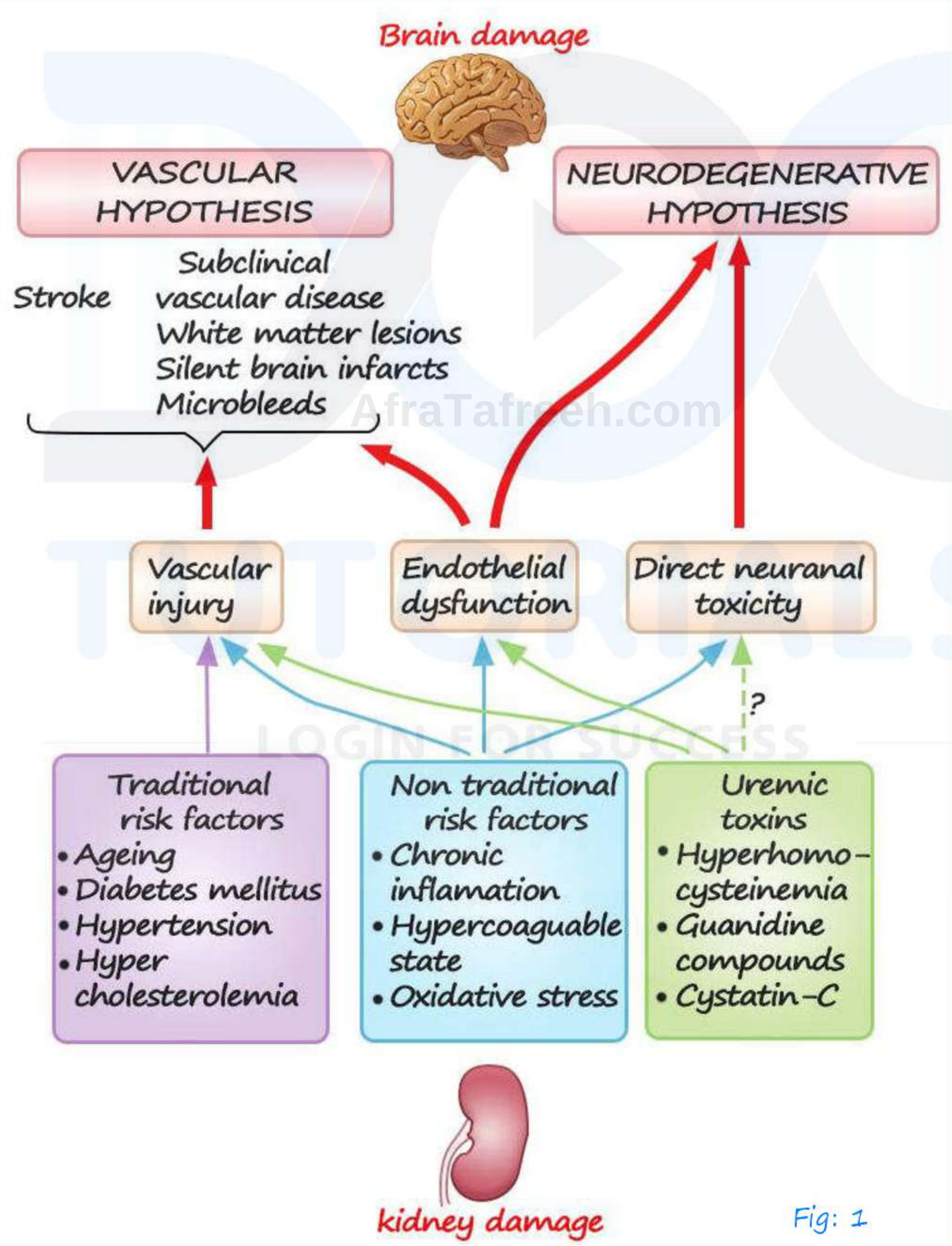

Fig: 1

- Can be due to vascular impact (or) neurodegenerative

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- Vascular impact can cause
  - Small vessel ischemic changes
  - Microinfarcts
  - Microbleeds

Manifestations 00:07:16

- Encephalopathy
- CVA
- Increased risk of opportunistic infections
  - Meningitis
  - Encephalitis
- Movement disorders → Myoclonus
- Cognitive impairment → Dementia
- Osmotic myelinolysis
- Peripheral neuropathy → Distal sensory and symmetric neuropathy
- Carpal tunnel syndrome
- Restless leg syndrome – urge to move the legs
  - Alteration in iron metabolism & dopaminergic transmission
- Myopathy
- Increased risk of developing thrombotic microangiopathy

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Encephalopathy	Presumed pathophysiology	Therapeutic or preventive measures
Uremic encephalopathy	Accumulation neurotoxins Disturbances in intermediary metabolism Hormonal disturbances	Dialysis or kidney transplantation
Wemnicke's encephalopathy Dialysis encephalopathy/ dementia	Thiamine deficiency Aluminum accumulation	Thiamine administration Use of aluminum-free dialysate Avoidance of aluminum-based phosphate binders Administration of deferoxamine
Rejection encephalopathy Hypertensive encephalopathy Dysequilibrium syndrome	Cytokine production due to the rejection process Cerebral vasogenic edema Reverse urea effect	increase Immunosuppressio n Antihypertensive treatment Self-limited

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	Intracellular acidosis in carabral cortex	
Fluid and electrolyte disturbances Drug toxicity	Increase Calcium, magnesium, sodium disturbances, osmolality Drugs metabolized or excreted by kidney Immunosuppressive drugs	Correction of electrolyte imbalance Dose reduction or cessation

- PRES
  - Posterior reversible encephalopathy syndrome
  - Result of uncontrolled HTN
    Cerebral edema-DDS.

TUTORIALS LOGIN FOR SUCCESS

BASIC STRUCTURE OF GLOMERULUS

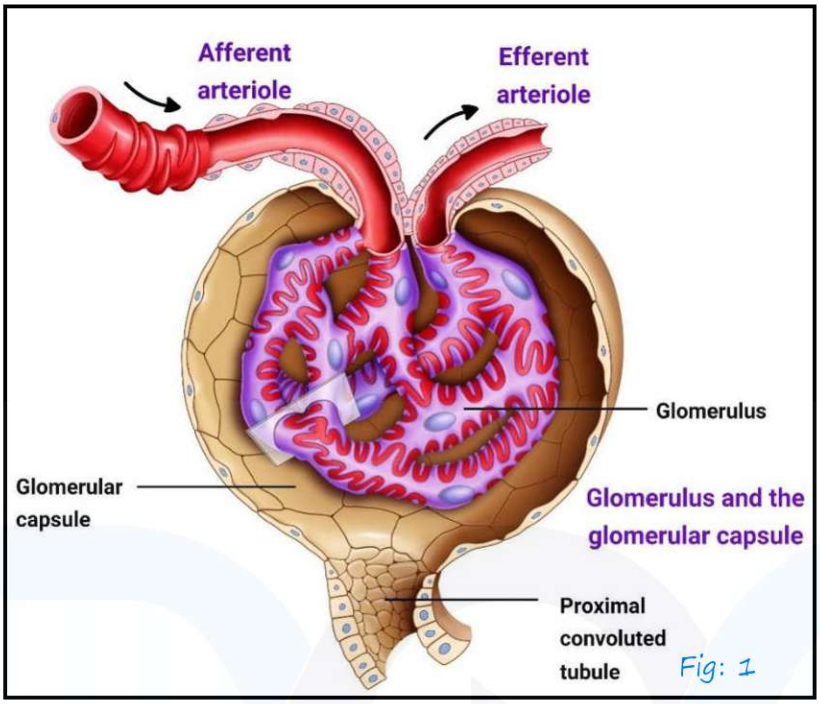

Fig: 1

- Bowman's capsule together with glomerulus makes the renal corpuscle
- Bowman's capsule has parietal layer and visceral layer

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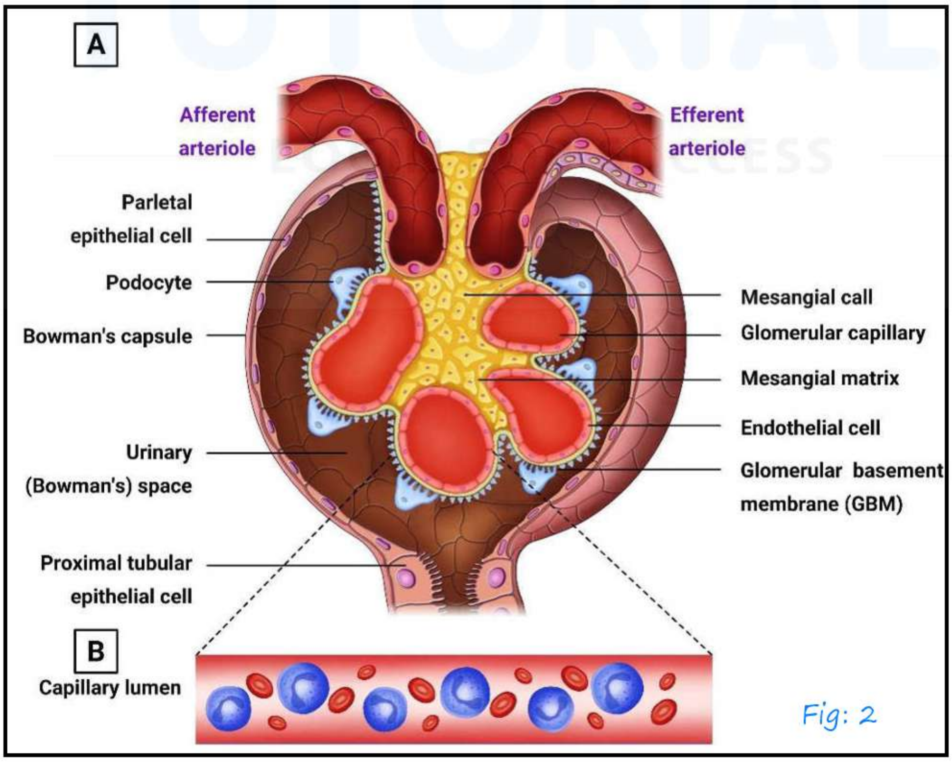

Fig: 2

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- Visceral layer of Bowman's capsule contains certain highly differentiated cells
  ↓
  - Podocytes → foot processes of podocytes are very closely linked to glomerulus
- Gaps in endothelial cells are known as Fenestrations

Components of Glomerulus 00:07:16

i. Capillary Endothelium
ii. Glomerular basement membrane
iii. Mesangium

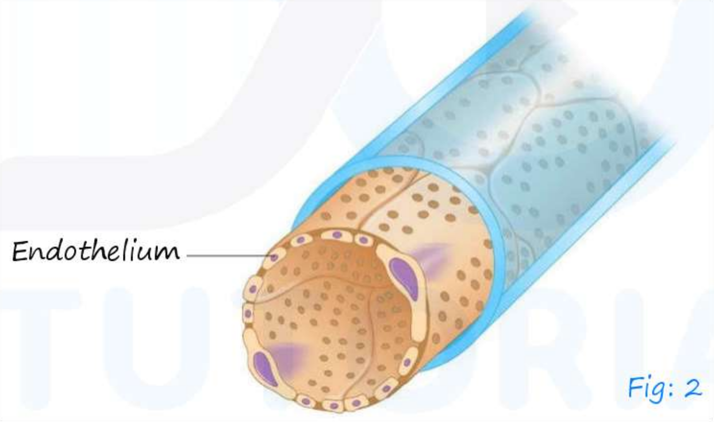

Fig: 2

- Endothelium → small pores ⊕ - Fenestrations

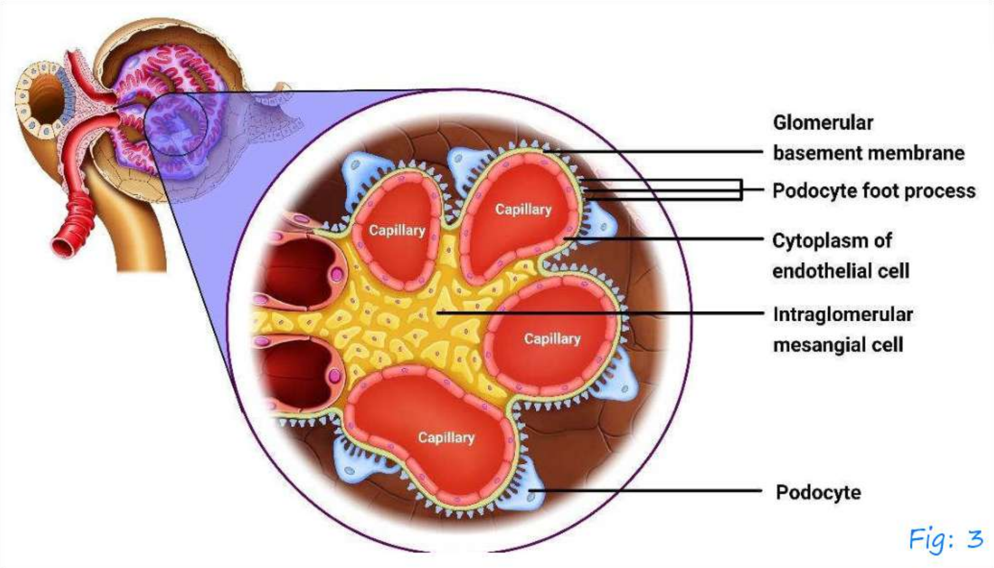

Fig: 3

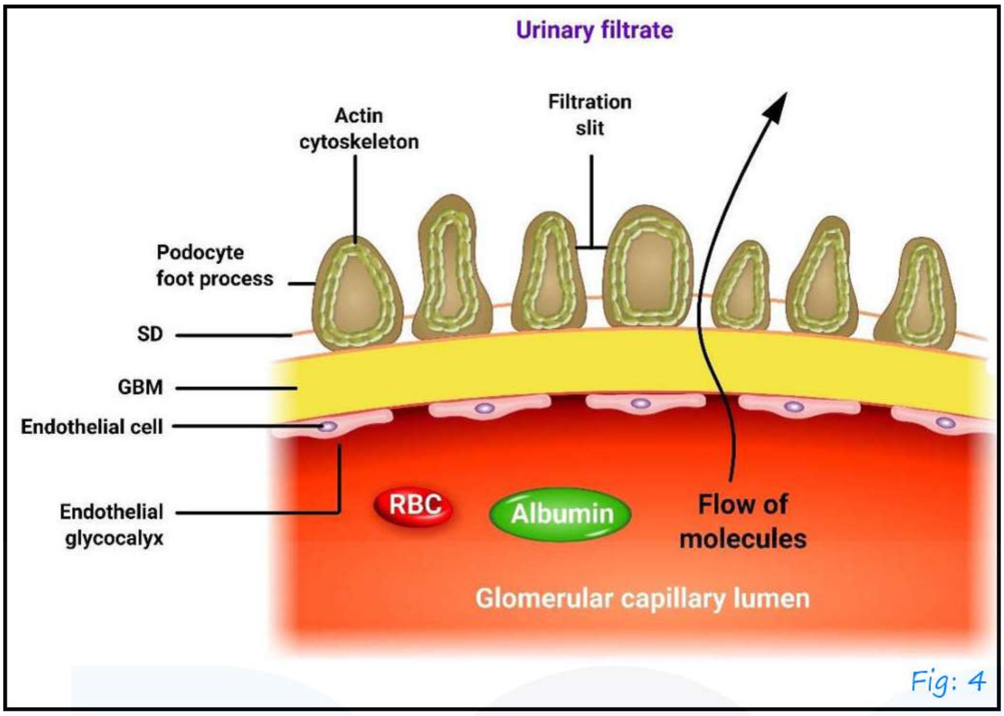

Fig: 4

Capillary Endothelium

- Negatively charge
- Endothelial glycocalyx – covering of glomerular endothelium

  ↓

  consists of sialoglycoproteins → hence negative charge
- Gap of fenestrations is 50-100nm

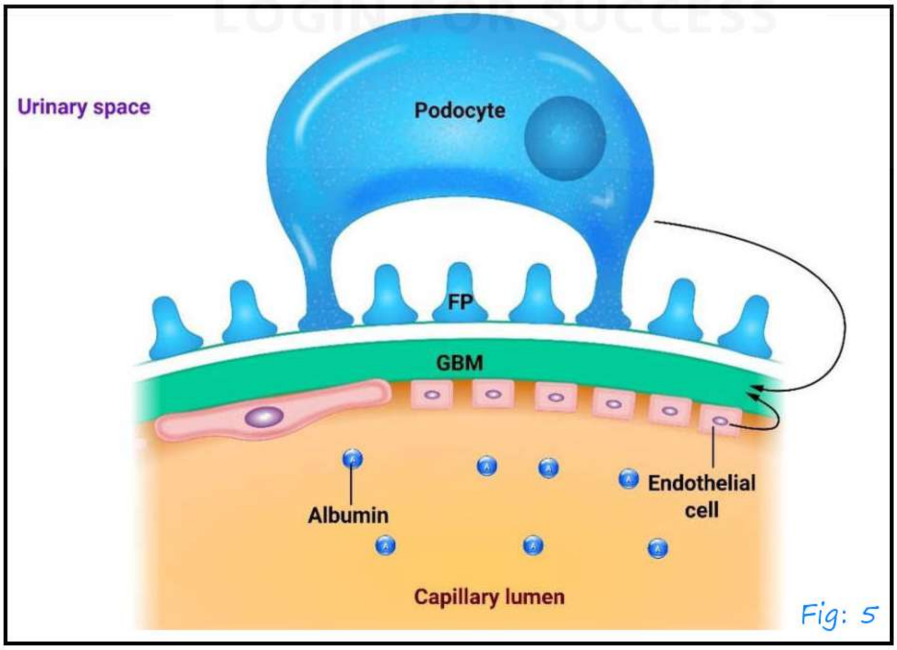

Fig: 5

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- GBM consists of – Collagen
  - Laminin
  - Heparin sulphate
- Glomerular basement membrane – also negatively charged
  ↓
  d/t heparin sulphate

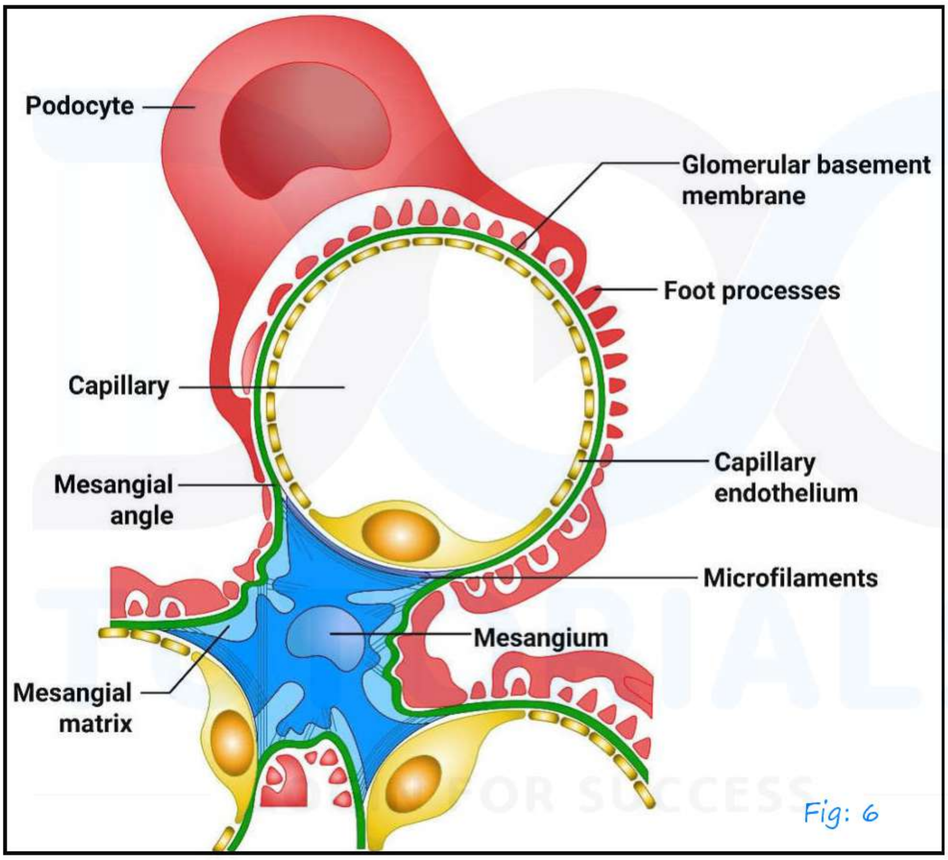

Fig: 6

Mesangium

- Consits of mesangial cells and mesangial matrix
- Microfilaments bind mesangium with glomerular basement membrane.
- GBM – effective contractility of mesangium

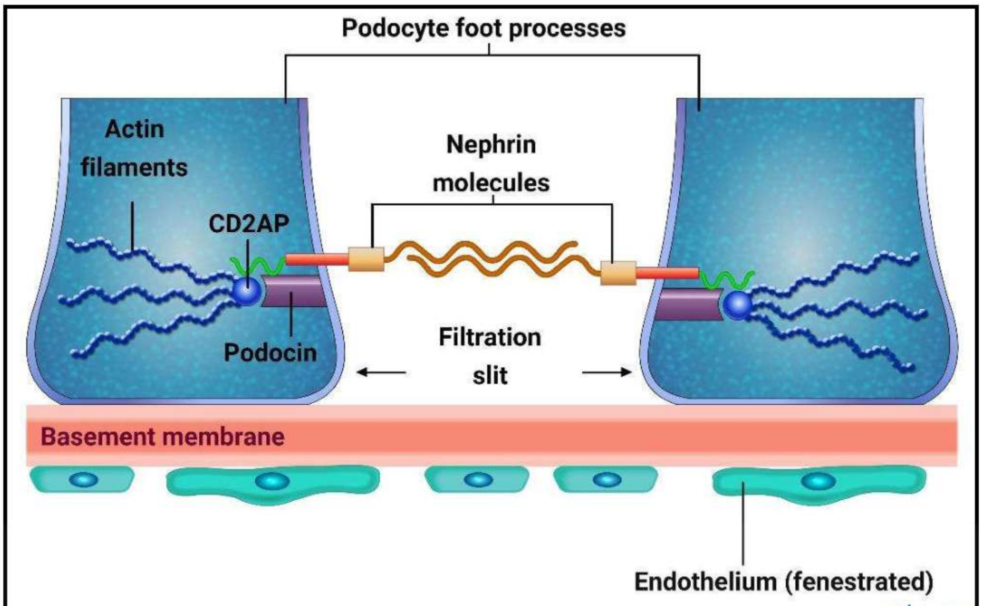

Fig: 7

Foot Processes

- Slit diaphragm (SD) bridges the gap between foot processes.

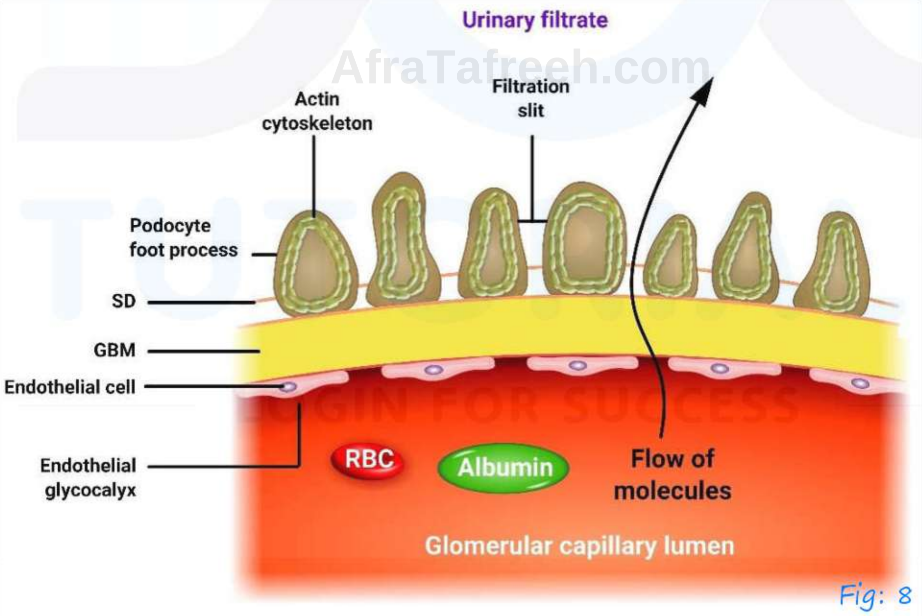

Fig: 8

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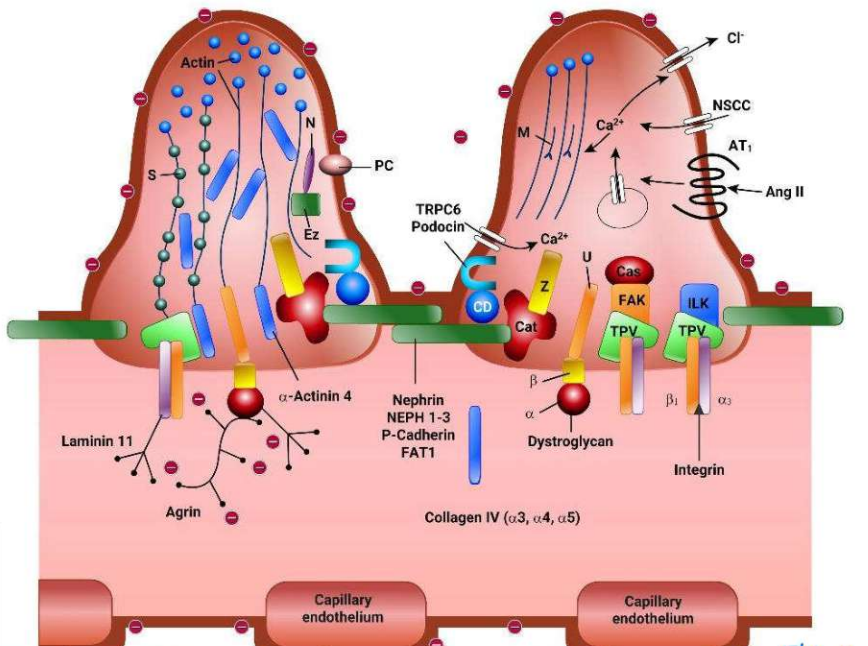

Fig: 9

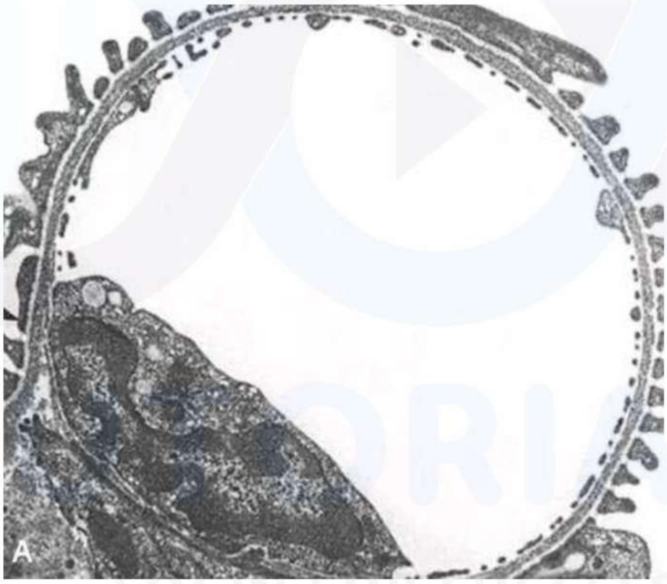

Fig: 10

CLINICAL MANIFESTATIONS OF GLOMERULAR DISEASES

Clinical manifestations 00:00:56

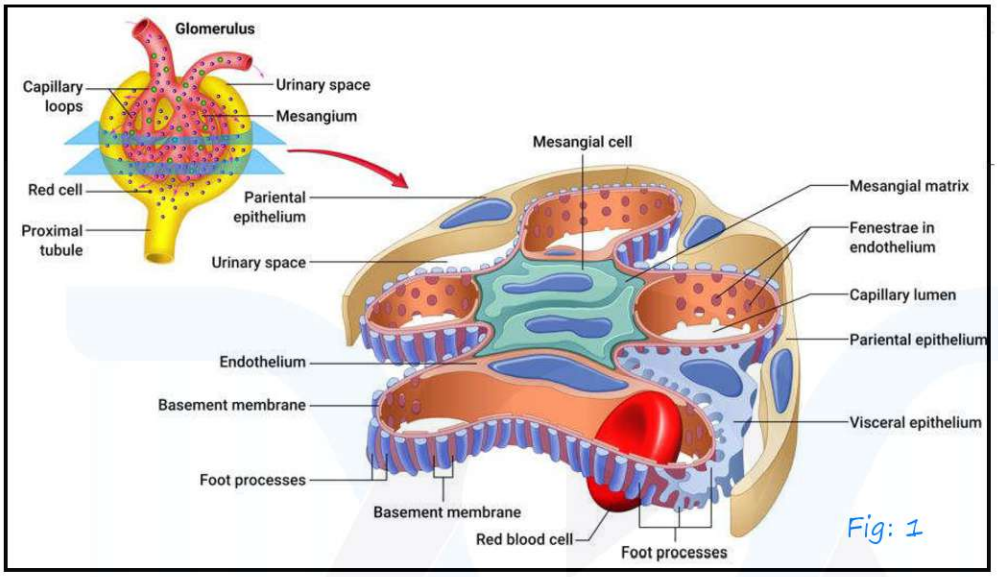

Fig: 1

Glomerular filtration barrier Fig: 2

- Glomerular basement membrane – trilammar structure

  ↓

  - Central – lamina densa
  - Outer – lamina rara externa
  - Inner – lamina rara interna

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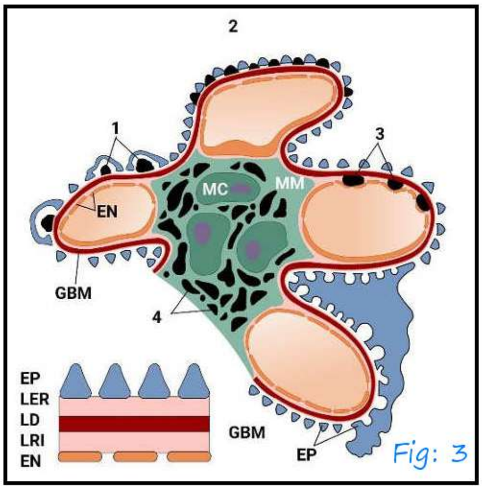

Fig: 3

- Antibody and immune complex formation

  ↓

  Immune complexes may be deposited @ various sites
- Depending on the site involved → manifestations vary

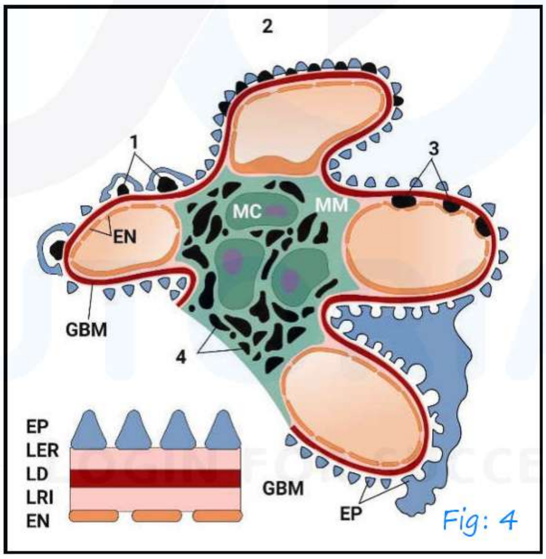

Fig: 4

i. Subepithelial immune complex deposits

ii. Membranous immune complex deposits

iii. Subendothelial immune complex deposits

iv. Mesangial immune complex deposits

6 patterns/ presentations 00:14:20

i. Asymptomatic

ii. Macroscopic hematuria

iii. Nephrotic hematuria

iv. Nephritic syndrome

v. Rapidly progressive glomerulonephritis

vi. Chronic glomerulonephritis

i. Asymptomatic

- Urine examination
- Microscope hematuria: ≥ 3 RBC/hpf in a spun urinary sediment
- 3000 rpm for 5 minutes
- Proteinuria
- Renal biopsy may be needed

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Rbc cast:

Fig: 5

ii. Macroscopic hematuria

- R/O urology causes

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iii. Nephrotic syndrome

a. proteinuria

- Nephrotic range proteinuria → 3.5g/24 hours
- 24 hours urinary sample collection
- Protein loss > 3.5 g/day ⎤ Nephrotic range proteinuria
- Albumin > 2.2g/day ⎦
- Spot sample estimation
- ALR (albumin creatinine ratio) > 2200mg albumin/ g 06 urinary creatinine

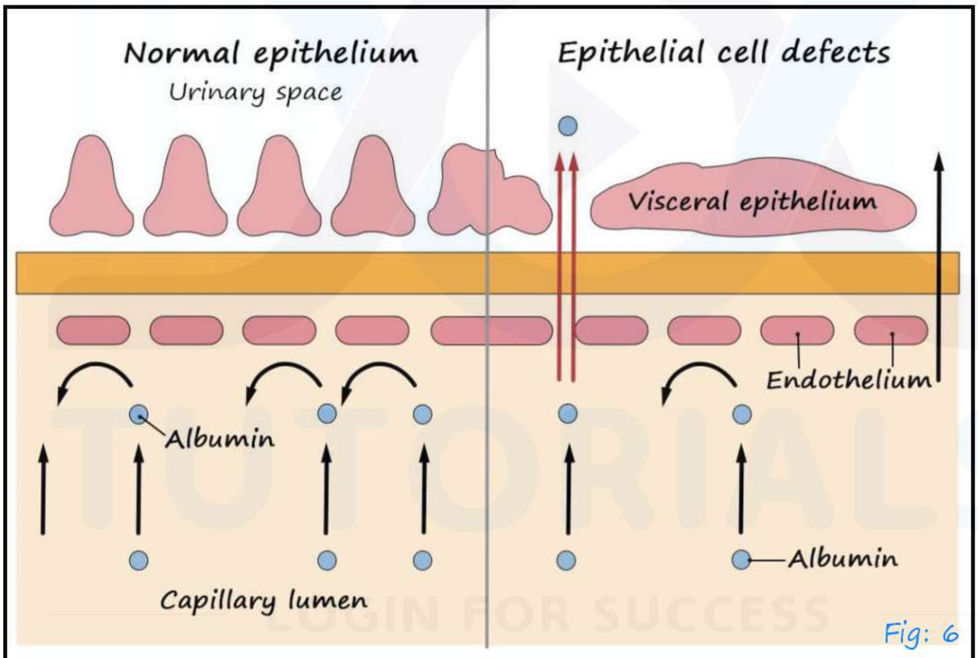

Fig: 6

- Flattening of visceral epithelium
- Proteins can leak through
- Proteinuria
- c/o frothing of urine
- non selective proteinuria
- selective proteinuria → MCD

b. Hypoalbuminemia

c. edema

- Decreases oncotic pressure
- Fluid enters extravascular compartment

  ↓

  Generalized edema (anasarca)

  ↓

  More pronounced in children
- Nephrotic syn → catabolic state
- Na^+ retention → edema

d. Hypercholesterolemia

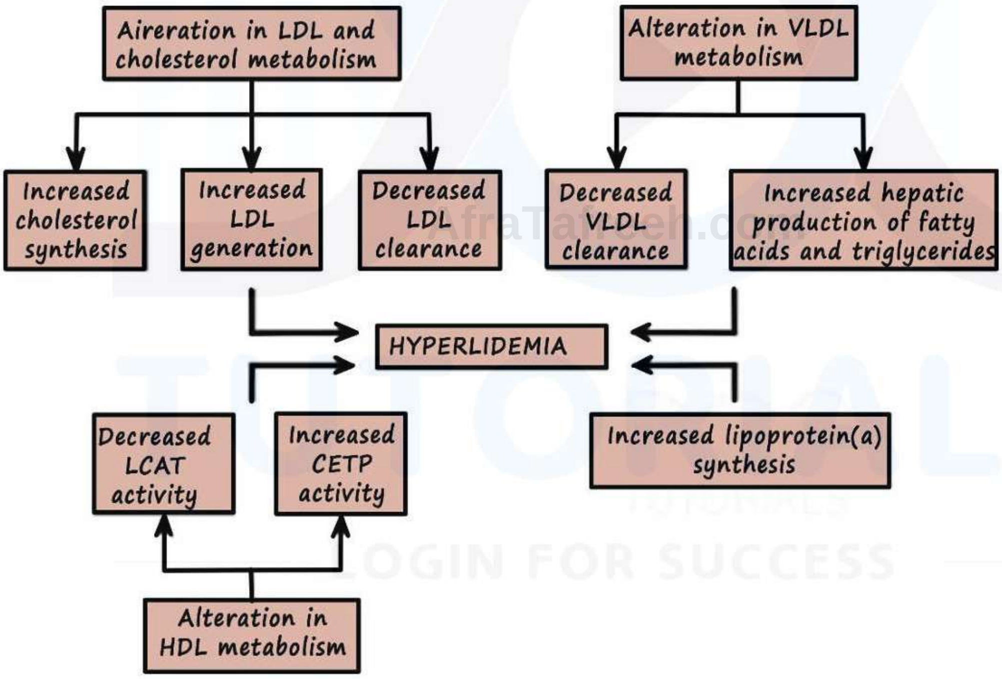

Fig: 7

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- Oval fat bodies

  ↓

  When examined under polarizing microscopy

  ↓

  Maltese cross appearance

- Patient with nephrotic syndrome has higher chance for coagulation abnormalties

Coagulation abnormalities 00:44:25

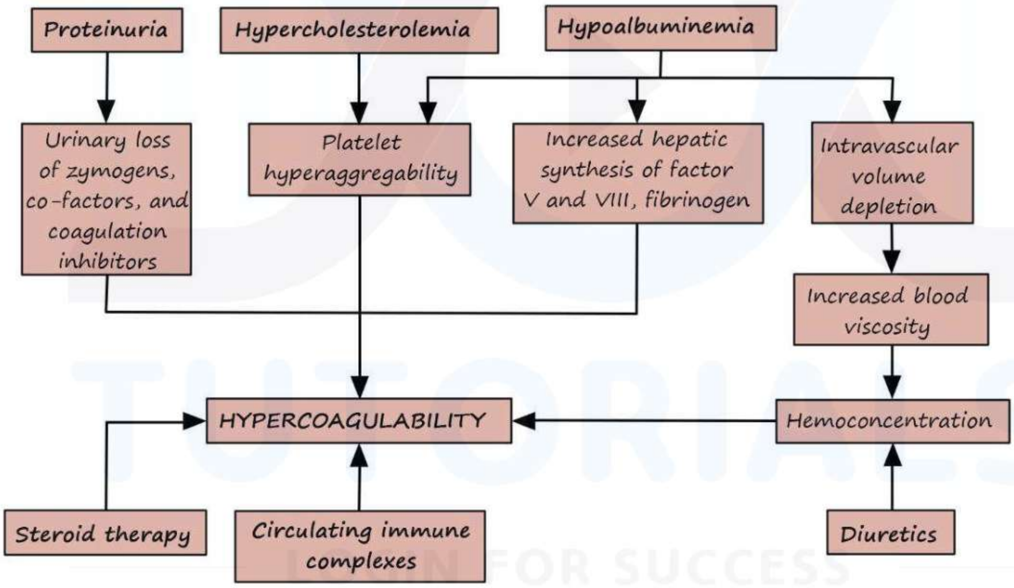

Fig: 8

meuhrackes nails Fig: 9

Xanthelesma Fig: 10

Etiology of Nephrotic Syndrome

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Primary Causes	Secondary Causes
Minimal change nephrotic syndrome	Systemic disease (diabetes, lupus)
Focal segmental Glomerulosclerosis (FSGS)	Infection (HIV, hepatitis B, hepatitis C)
Membranous Nephropathy (MN)	Pre-eclampsia
Membranoproliferative Glomerulonephritis (MPGN)	Certain drugs and toxins
IgA nephropathy	Congenital due to intrauterine infections
Hereditary (Finish-type, Denys-Drash, Frasier)	

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iv. Nephritic presentation

- Hematuria (cola colored urine)
- Olioguria
- Proteinuria
- Edema
- Intravascular volume overload:

Accure pulmonary adema

HTN

Common Glomerular Disease presenting as nephritic syndrome		
Disease	Associations	Serologic tests
Poststreptococcal glomerulonephritis	Pharyngitis, impetigo	Antistreptolysin titer, streptozyme antibody
Other postinfectious disease		
Endocarditis	Cardiac murmur	Blood cultures, C_3 decreases
Abscess	-	Blood cultures, C_3, C_4 normal or increased
Shunt	Treated hydrocephalus	Blood cultures, C_3 Decreases
IgA nephropathy	Upper respiratory or gastrointestinal infection	Serum IgA increases
Lupus nephritis	Other multisystem features of lupus	Antinuclear antibody, anti-double stranded DNA antibody, C_3 decreases, C_4 decreases.

Differentiation between Nephrotic syndrome and Nephritic syndrome

Typical features	Nephrotic	Nephritic
Onset	Insidious	Abrupt
Edema	++++	++
Blood pressure	Normal	Raised
Jugular venous pressure	Normal/Low	Raised
Proteinuria	++++	++
Hematuria	May/may not occur	+++
Red blood cell casts	Absent	Present
Serum	Low	Normal/slightly reduced

v. RPGN

- Progresses from days to weeks

Glomerular disease presenting as rapidly progressive glomerulonephritis		
Disease	**Associations**	**Serologic tests**
Goodpasture syndrome	Lung hemorrhage	Anti-glomerular basement membrane antibody (occasionally antineutrophil cytoplasmic antibody [ANCA] present)
Vasculitis		
Granulomatosis with polyangiitis (Wegener granulomatosis)	Upper and lower respiratory tract involvement	Cytoplasmic ANCA
Microscopic polyangiitis	Multisystem involvement	Perinuclear ANCA
Pauci-immune crescentic glomerulonephritis	Renal involvement only	Perinuclear ANCA
Immune complex Disease		
Systemic lupus erythematous	Other multisystem features of lupus	Antinuclear antibody, anti-double stranded DNA antibody, C_3 decreases, C_4 decreases

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Poststreptococcal glomerulonephritis	Pharyngitis, impetigo	Antistreptolysin titer, streptozyme antibody
IgA nephropathy; IgA vasculitis (Henochschonlein purpura [HSP])	Characteristic Rash ± Abdominal pain in HSP	C_3 decreases, C_4 normal serum IgA increases (30%) C_3 and C_4 normal
Endocarditis		
	Cardiac murmur; Other systemic features of bacteremia	Blood cultures ANCA (occasionally) C_3 decreases, C_4 normal

vi. Chronic glomerulonephritis

- CKD
- Small contracted kidney
- Cortico medullary differentiation is lost

Asymptomatic

- Proteinuria 150mg to 3g per day hematuria >2 red blood cells per high-power filed in spun urine or > 10 x 10^6 cells/liter (red blood cells usually dysmorphic)

Macroscopic hematuria

- Brown/red painless hematuria (no clots); typically coincides with intercurrent infection.
- Asymptomatic hematuria ± proteinuria between attacks

Nephrotic syndrome

- Proteinuria: adult > 3.5 g/day; child >40 mg/h per m^2.
- Hypoalbuminemia <3.5 g/dl Edema
- Hypercholesterolemia
- Lipiduria

Nephritic syndrome

- Oliguria
- Hematuria: red cell casts
- Proteinuria: usually <3 g/day
- Edema
- Hypercholesterolemia
- Lipiduria

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Rapidly progressive glomerulonephritis

- Renal failure over days/weeks
- Proteinuria: usually <3 g/day
- Hematuria: red cell casts
- Blood pressure often normal
- May have other features of vasculitis

Chronic glomerulonephritis

- Hypertension
- Renal impairment
- Proteinuria often >3 g/day
- Shrunken smooth kidneys

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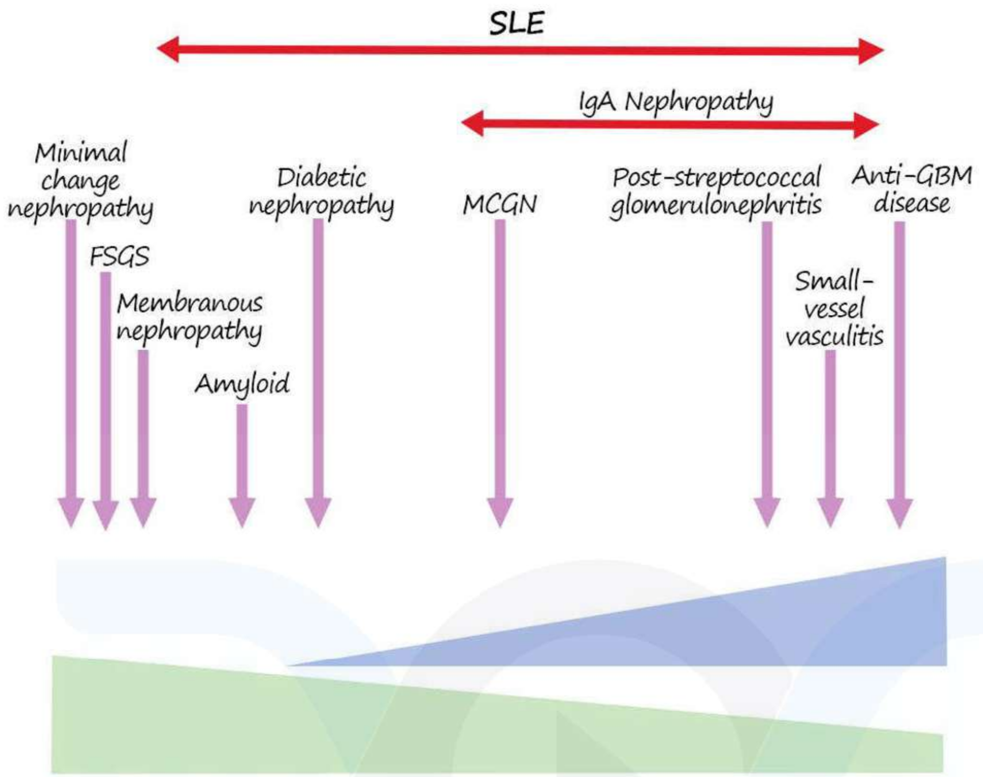

MINIMAL CHANGE DISEASE

Minimal change disease (MCD) 00:00:40

- Podocytopathy
- There occurs effacement of foot processes of podocytes

  ↓

  Flattening

  Fusioning

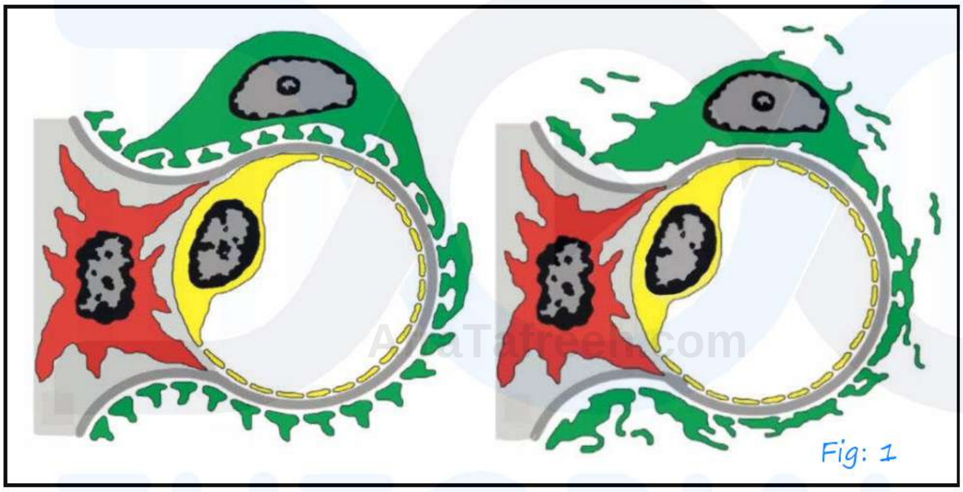

Fig: 1

- Age group: 2-6 years
- Males > females

Clinical Feature 00:06:00

- Nephrotic syndrome
- MCD → 70-90% nephrotic syndrome in children (m/c/c)

  → 10-15% NS in adults

  - Generalized edema (anasarca)

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- Ascites
- HTN
- Hematuria
- Raised creatinine

Uncommon adult MCD may have these features (Ascites, HTN, Hematuria)

Complications 00:11:20

- Infections → pneumococcal peritonitis
- Thrombosis
- Rickets
- Hypovolemic shock
- Growth retardation

2° minimal change d/s 00:14:44

i. Malignancies
   - Hodgkins lymphoma
   - Mycosis fungoides (cutaneous T cell lymphoma)
   - Chronic lymphocytic leukemia (CLL)
   - Usually MPGN

ii. Thymomas

iii. Drugs
   - SAIDS
   - INF-α
   - Lithium → chronic interstitial nephritis
   - Gold → membranous nephropathy

iv. Allergies
   - Atopic dermatitis

- House dust
- Pollen
- Insect bite
- Immunization

Evaluation 00:20:00

- Same as nephrotic syndrome
- Biopsy (only adults)

Biopsy in children

- Age < 1 year
- Steroid resistant
- Low complement levels

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Biopsy

- Light microscopy
- Immunofluorescence
  } Normal
- Electron micrscopy

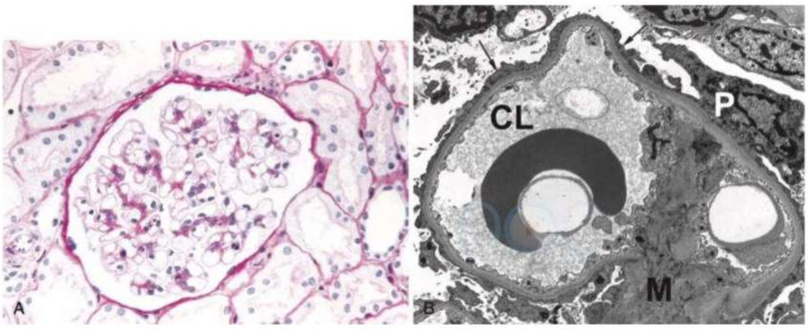

Fig: 2

Light microscopy   Electron microscopy

- Some cases may show IGM mesangial deposits

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Treatment 00:28:00

- Oral prednisolone
- 2mg/kg/day (children)
- 1mg/kg/day (adults)
- 6 +6 regimen
- 6 weeks → full dose
- 6 weeks → tapered dose

MCG – Nil lesion

lipoid nephrosis

- Good remission

↓

No protein in 3 consecutive urine samples

- Fluid restriction

↓

Intake = urine output + irreversible loss

- Salt restriction → no added salt
- Protein → high normal protein intake

In MCD – selective proteinuria

Sometimes albumin supplementation

- Diuretics → Cautious

- Always chance of relapse due to infection

↓

Treatment – Steroids (2+4 weeks regimen)

Frequent relapses

- Cyclophosphamide

- Cyclosporine/tacrolimus

Steroid dependence

↓

- 2 or more relapses with on alternate day steroids
- 2 or more relapses with on 2 weeks of stopping steroids
- Calcineurin inhibitors

Steroid resistance

↓

- In children → 4 weeks of steroids

  ↓

  not able to achieve remission
- In adults → 4 months of steroids

  ↓

  not able to achieve remission
- Calcineurin inhibitors

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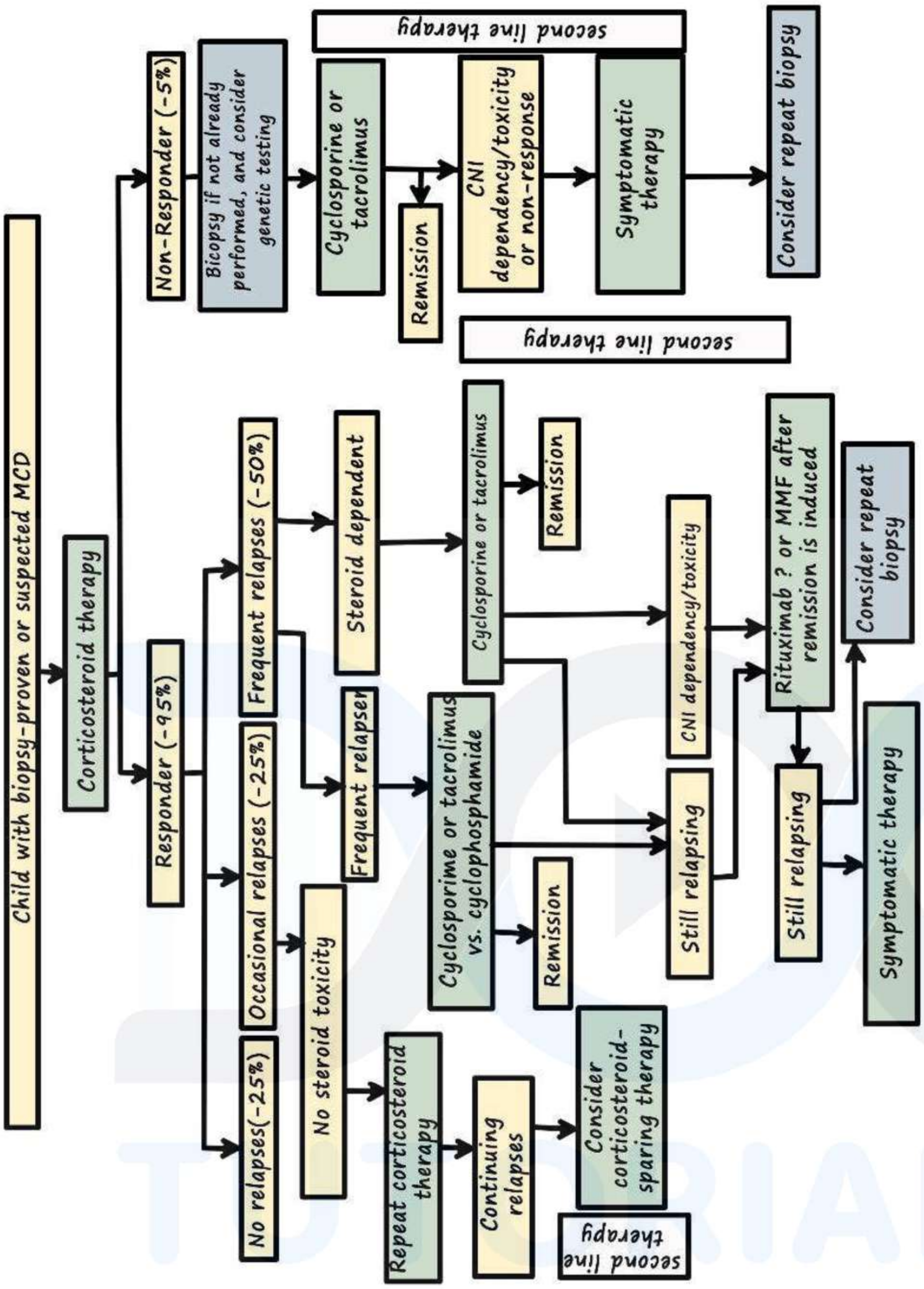

FSGS

Nephrology – Glomerular d/s 00:00:30

- Focal segmental glomerulosclerosis
- Most common cause of nephrotic syndrome in adults
- Podocytopathy
- Detachment of podocytes (+)
- There is focal and segmental glomerulosclerosis

  ↓

  <50% glomeruli

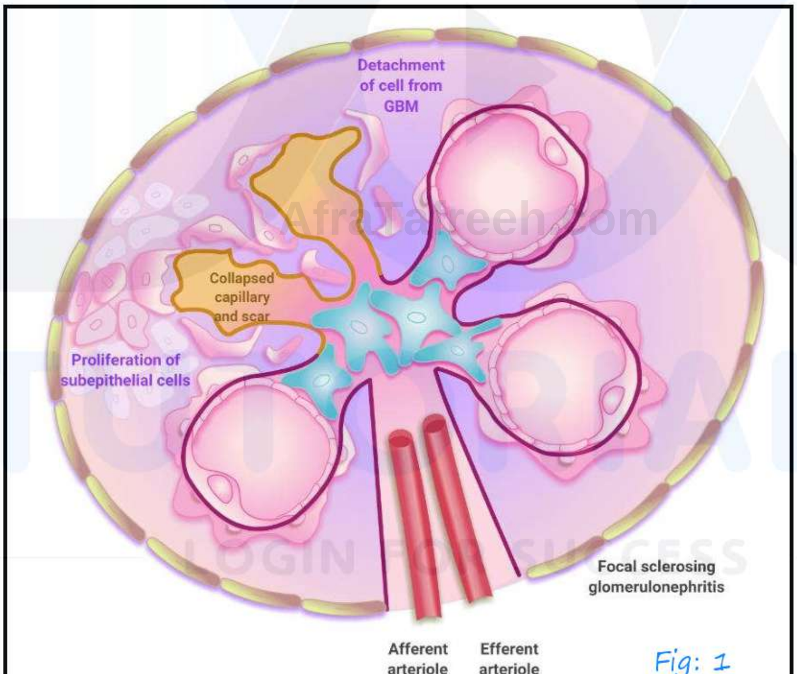

Fig: 1

- There is some sclerosis between podocyte and epithelium
- Classification
  - Primary
  - Secondary
- Causes

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Focal Segmental Glomerulosclerosis 00:06:10

- Primary focal segmental glomerulosclerosis
- Secondary focal segmental glomerulosclerosis
- Viruses: HIV/hepatitis B/parvovirus
- Hypertensive nephropathy
- Reflux nephropathy
- Cholesterol emboli
- Drugs: Heroin/analgesics, bisphosphonates/ecstasy
- Oligomeganephronia
- Renal dysgenesis
- Alport's syndrome
- Sickle cell disease
- Lymphoma
- Radiation nephritis
- Familial podocytopathies
- NPHS1 mutation/nephrin
- NPHS2 mutation/podocin
- TRPC6 mutation, cation channel
- ACTN4 mutation/actinin
- α-Galactosidase A deficiency/Fabry's disease
- N acetylneuraminic acid hydrolase deficiency/nephrosialidosis
- Drugs
- Sirolimus
- Bisphosphonates – Pamidronate
- Interferon

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Morphological variants 00:10:00

Classical variant:not otherwise specified

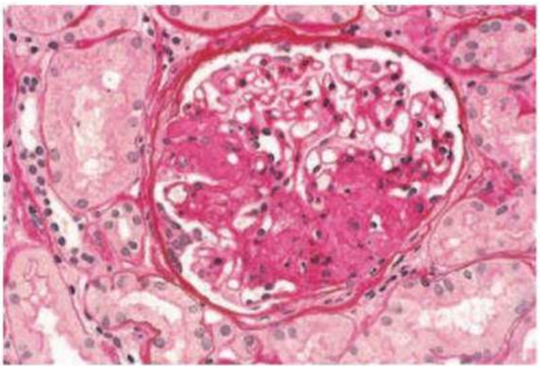

Fig: 2

Perihilar variant:

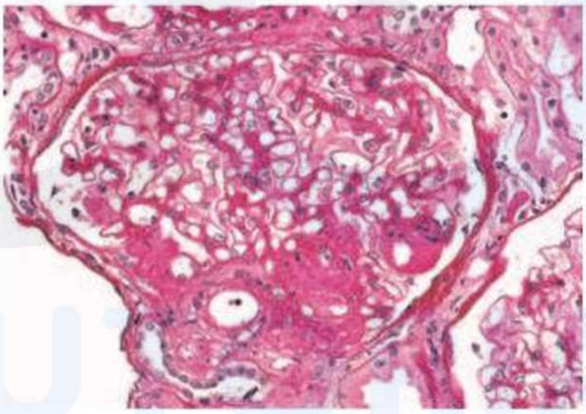

Fig: 3

Cellular variant: endocapillary proliferation

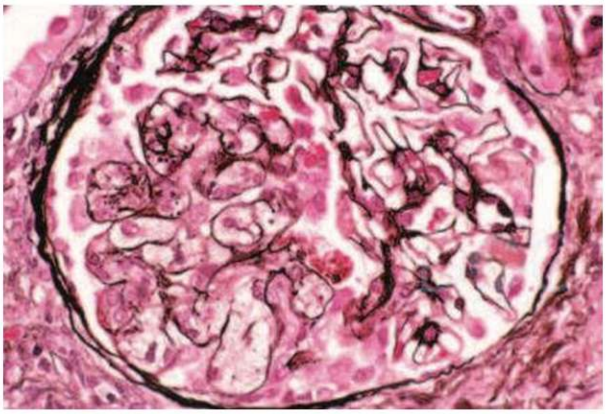

Fig: 4

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Collapsing variant:

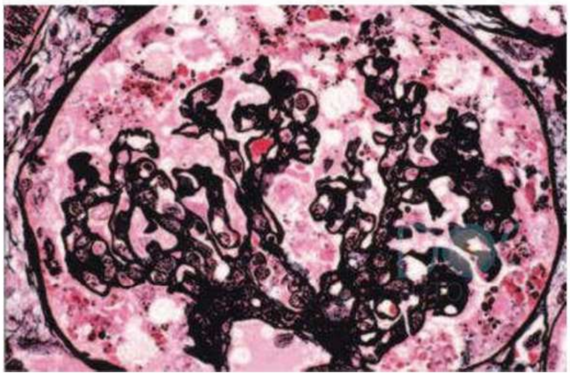

Fig: 5

- Collapse and retraction of glomeruli
- Poor prognosis
- Ass.with hiv

Tip lesion variant:

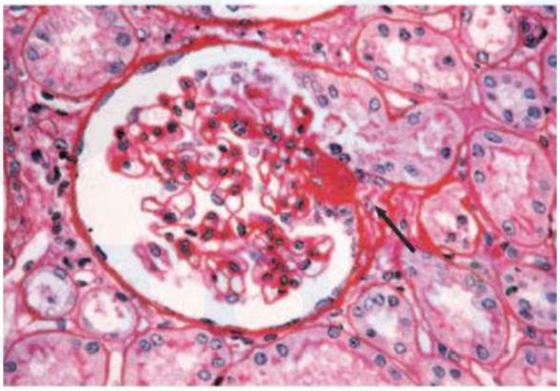

Fig: 6

- Lesion at origin of proximal tubule
- Good prognosis

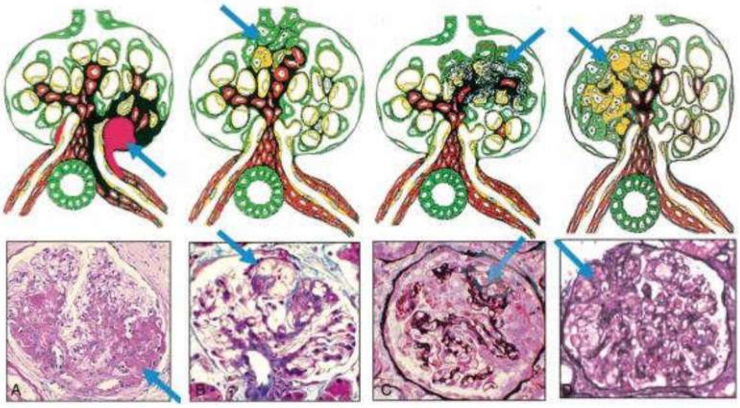

Fig: 7

Clinical presentation 00:18:52

- Presents as nephrotic syndrome
- May have associate
- Hypertension
- raised serum creatinine
- Hematuria
- Can proceed to chronic kidney disease
- Can present in children also

Investigations

- Rule out 2° causes
- Biopsy

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Treatment 00:23:00

- 1° FSGS
  - Steroids
  - Oral prednisolone – 1mg/kg/day
  - Longer duration of treatment
  - ACE inhibitors/ARB's → reduce proteinuria
  - Statins
  - Cyclosporine
  - Mycophenolate mofetil
- 2° FSGS
  - No role for steroids & immunosuppression

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MEMBRANOUS NEPHROPATHY

- Also called as Membranous Glomerulonephritis
- Also a podocytopathy
- Age of presentation - 30-50 years
- M>F (2:1)
- Most common cause Nephrotic syndrome in elderly(>60yrs) – Membranous nephropathy

Classification 00:02:54

- Primary
  - Almost 70% cases are anti PLA_2 receptor
  - Anti-thrombospondin
- Secondary

Causes of Secondary Membranous Nephropathy 00:03:20

1. Infections
   - Hep B
   - Hep c
   - Syphilis
   - Schistosomiasis
   - Malaria
   - Leprosy
2. Malignancies –
   - Ca Breast

- Ca colon
- Ca Stomach
- Ca Lung
- Ca Neuroblastoma

3.Drugs

- Gold
- Mercury
- d-penicillamine
- NSAIDS

4.Autoimmune disorders

- Hashimoto's thyroiditis
- SLE
- Rheumatoid Arthritis
- Sjogrens syndrome
- Sarcoidosis
- Ig G4 related disorders

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Membranous Glomerulonephritis

- Primary/idiopathic membranous glomerulonephritis
- Secondary membranous glomerulonephritis
- Infection: Hepatitis B and C, syphilis, malaria, schistosomiasis, leprosy, filariasis
- Cancer: Breast, colon, lung, stomach, kidney, esophagus, neuroblastoma
- Drugs: Gold, mercury, penicillamine, nonsteroidal anti-inflammatory agents, probenecid

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- Autoimmune diseases: Systemic lupus erythematosus, rheumatoid arthritis, primary biliary cirrhosis, dermatitis herpetiformis, bullous pemphigoid, myasthenia gravis, Sjögren's syndrome, Hashimoto's thyroiditis
- Other systemic diseases: Fanconi's syndrome, sickle cell anemia, diabetes, Crohn's disease, sarcoidosis, Guillain-Barré syndrome, Weber-Christian disease, angiofollicular lymph node hyperplasia

Pathology 00:09:06

Fig: 1

- Stage I - characterised by subepithelial deposits
- Stage II Basement membrane sends out certain projections in between these deposits → spikes of basement membrane

- Stage III – Immune complex deposits are inside membrane the basement membrane
- Stage IV – Increase in glomerular basement membrane thickness & Immune complex deposits appear as lucencies.

Clinical Features 00:13:45

- Nephrotic syndrome – non selective proteinuria
- Hematuria (microscopic)
- HTN
- ↑ serum creatinine
- Highest propensity for thrombosis
- 1/3rd cases have spontaneous remission
- 1/3rd case relapsing nephrotic syndrome
- 1/3rd chronic kidney disease

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Biopsy: 00:17:40

- Light microscopy:

Fig: 2

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- Glomerular basement membrane thickness increased
- Immunofluorescent microscopy: Diffuse granular deposits of IgG & C3
- Electron microscopy →

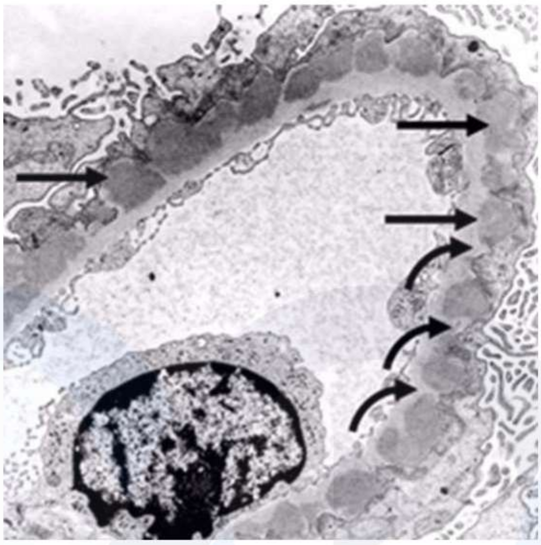

Fig: 3

- Straight arrow Immune complex deposits
- Curved arrow Basement spikes

Treatment 00:21:20

- ACE inhibitors
- Statins
- 1° membranous nephropathy ↓ immunosuppression
- Steroids + Cyclophosphamide
- Cyclosporine
- Mycophenolate mofetil
- Rituximab

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MEMBRANO PROLIFERATIVE GLOMERULO NEPHRITIS

Syndrome

i. Mesangio capillary glomerulonephritis
ii. Lobar glomerulonephritis

- Immune mediated glomerulonephritis
- Glomerular basement thickening
- Mesangial proliferation
- Lobar glomerular tuft architecture

Classification

- **Primary** → Very rare
- **Secondary**

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Secondary causes of MPGN

- Associated with infection
  - Hepatitis B and C
  - Visceral abscesses
  - Infective endocarditis
  - Shunt nephritis
  - Quartan malaria
  - Schistosoma nephropathy
  - Mycoplasma infection

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- Associated with rheumatologic disease
  - Systemic lupus erythematosus
  - Scleroderma
  - Sjogren syndrome
  - Sarcoidosis
  - Mixed essential cryoglobulinemia with or without hepatitis C infection
  - Anti smooth muscle syndrome

- Associated with malignancy
  - Carcinoma
  - Lymphoma
  - Leukemia

- Associated with an Inherited disorder
  - α_1 – antitrypsin deficiency
  - Complement deficiency (C2 or C3), with or without partial lipodystrophy

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Classification based on ultra-structure

MPGN Type I
↓
Immune complex deposits predominantly in subendothelial and mesangial regions

MPGN Type II
↓
Mesangial + intramembranous deposits

MPGN Type III
↓
Predominantly subepithelial
+
Intramembranous
+
Subendothelial deposits

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Mayo classification → based on pathology

Type I
↓
Immune complex mediated ± complement deposition

Type II
↓
Complement mediated

Alternate pathway

Scanty immune complex deposits

C_3 glomerulopathy

Intramembranous deposit
↓
Dense deposit disease

No IMD

C_3 glomerulonephritis

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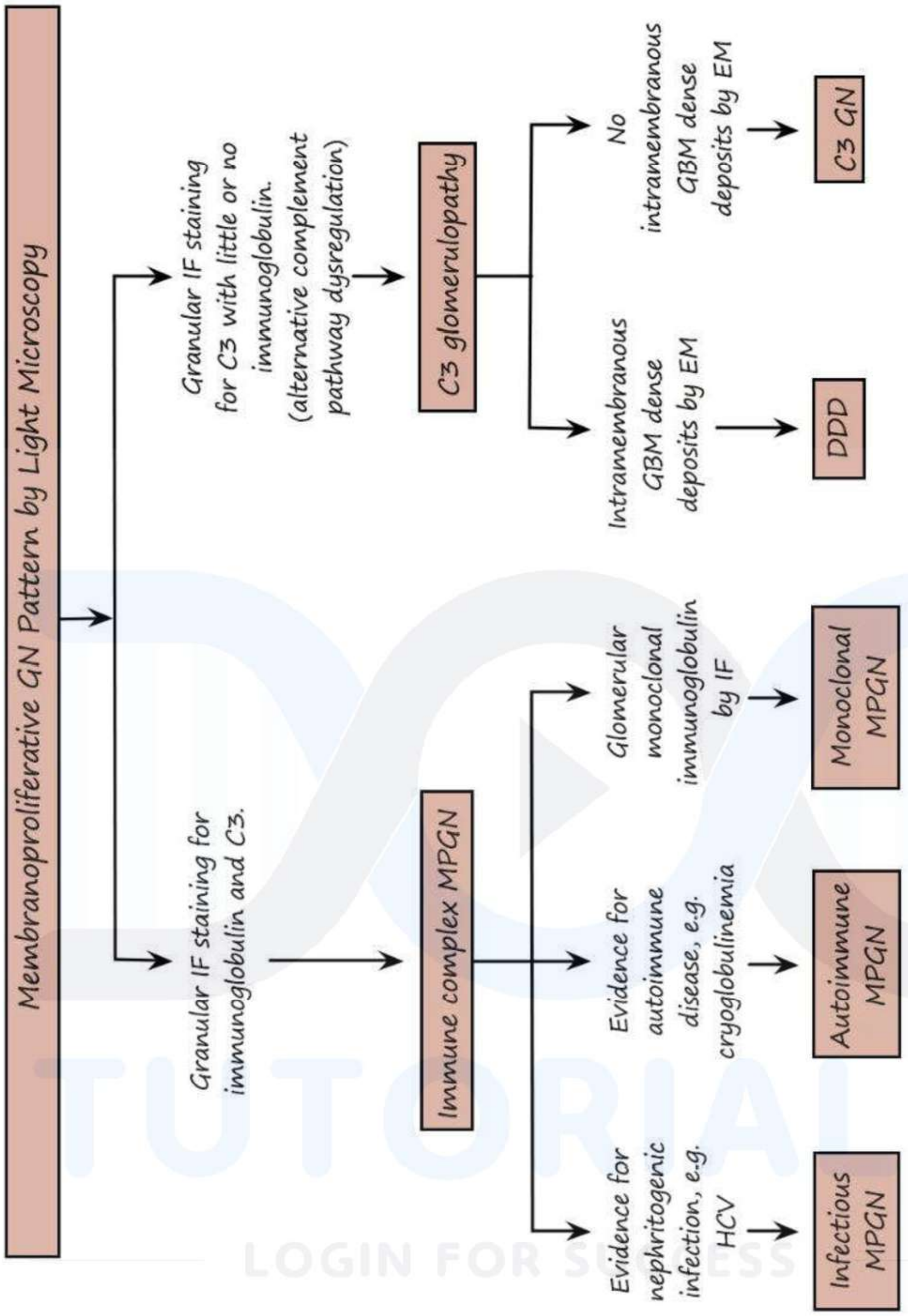

Clinical features 00:16:40

- Nephrotic syndrome
- Nephritic syndrome
- Nephrotic + nephritic
- RPGN
- CGN (Chronic glomerulonephritis)

Investigations

- Biopsy

Light microscopy

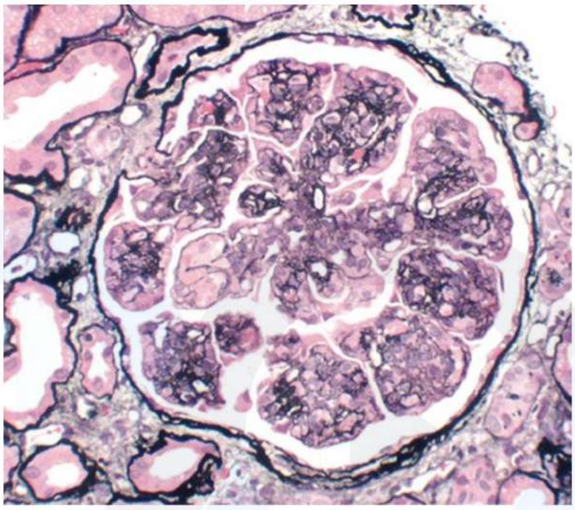

Fig: 1

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- Mesangial proliferation
- Some endocapillary proliferation
- Lobar architecture of glomerular tufts

- Immunofluorescence – Type I – IgG + IgM deposits ± C_3
  - Type II – C_3 deposition

- Electron microscopy → GBM splitting – Tram track appearance

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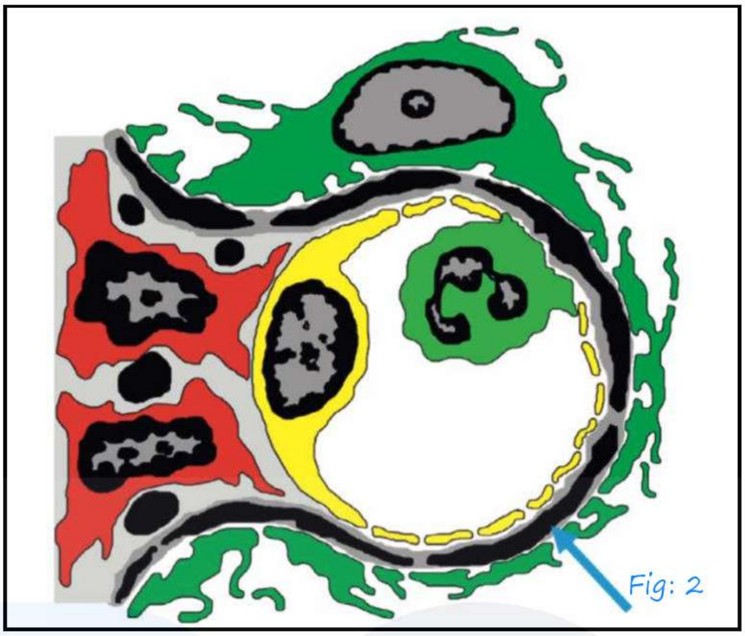

Treatment 00:22:30

- 1° MPGN – steroids
- 2° MPGN – Tract underlying cause .
- ACE inhibitors/ ARB's

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IgA NEPHROPATHY

- Most common cause of primary glomerular disorder
- Also, k/a Berger's disease
- Has several overlapping features with Henoch Schoenlein Purpura (HSP) → IgA vasculitis?

Pathogenesis 00:02:20

- IgA secretory form in MALT
- Problem lies in polymeric Ig A, secretory form present in MALT
- Defective galactosylation of polymeric IgA,
- Certain antibodies IgG Ab against Ig A,
- Immune complex formation
- Immune complex goes to kidney and deposited in mesangium

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Classification: 00:06:50

- Primary → Idiopathic
- Secondary familial

Secondary causes

1.Rheumatoid arthritis

2.Sjogren's syndrome

3.Relapsing polychondritis

4.Ankylosing spondylitis

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5.Reactive arthritis

6.Infections → HIV, toxoplasmosis and HBV

7.Celiac disease

8.Dermatitis herpetiform

9.Liver cirrhosis

10. NASH

Clinical Features 00:10:40

- Most common presentation - macroscopic haematuria
- Classical age group-2nd and 3rd decade
- M>F
- May be asymptomatic → Incidentally found to microscopic hematuria
- Nephrotic syndrome o chronic glomerulonephritis
- Hematuria alw IgA nephropathy - Syn pharyngitis hematuria
- patient may have URTI → hematuria
- 30% individuals of Ig A nephropathy – spontaneous remission
- 30% individuals of Ig A nephropathy - Episodic hematuria with preserved renal function
- 30% individuals of Ig A nephropathy - chronic kidney disease

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Investigation 00:16:10

- Serum IgA raised in 50% cases
- Serum complements levels normal
- Biopsy

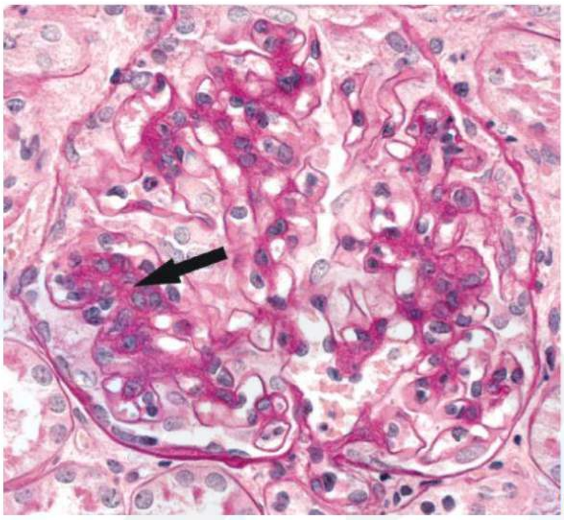

Fig: 1

- Light microscopy - mesangial expansion & hypercellularity

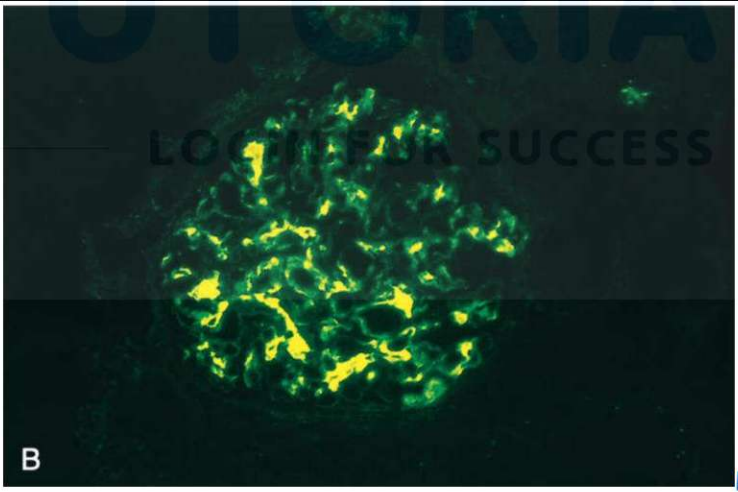

Fig: 2

Immunofluorescence
↓
IgA deposits

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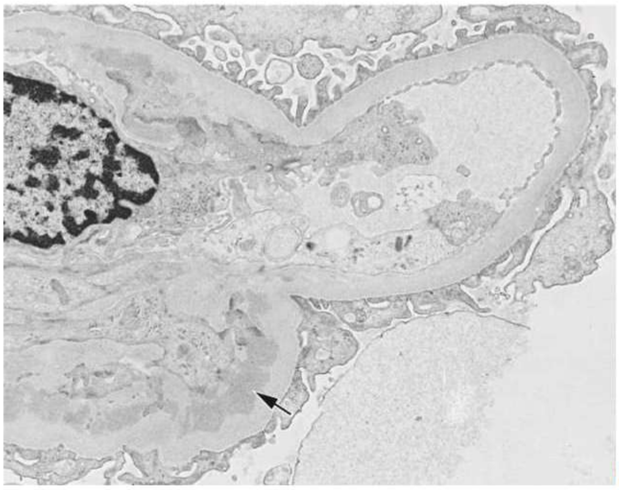

Fig: 3

Electron microscopy
↓
election dense deposits in mesangium

Treatment 00:21:12

- Manage HTN → ACEI /ARBS
- Steroids → Nephrotic syndrome presentation
- RPGN
- 6 months of conservative management proteinuria > 1g/day.

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Prognostic markers at presentation in immunoglobulin A nephropathy	
Clinical	Histopathologic
Poor prognosis • Hypertension • Renal impairment • Severity of proteinuria • Smoking • Hyperuricemia • Gross obesity • Long duration of preceding symptoms • Increasing age	• Mesangial hypercellularity • Endocapillary proliferation • Segmental glomerulosclerosis • Tubular atrophy • Interstitial fibrosis • Capillary loop IgA deposits • Crescents (Controversial)
Good prognosis Recurrent macroscopic hematuria	
No impact on prognosis • Gender • Serum IgA level • Intensity of IgA deposits	

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PSGN

- PSGN – Post Streptococcal Glomerulonephritis
- Term used know is infection related glomerulonephritis (IRGN)
  - Children (2-14 years) → Group A β hemolytic streptococcal infection
  - Adults (>60years) → MRSA diabetes
- Nephritogenic strains of group A β hemolytic streptococci
  - Streptococcal pyrogenic exotoxin E (major antigen) (SPEB)
  - Nephritis associated plasmin receptor (NAPIR)
    - i. Skin infection – Impetigo → Lag period is over 2-6weeks
    - ii. Pharyngitis → Lag period is over 1-3weeks

Pathology 00:10:32

- Acute endocapillary glomerulonephritis
  - Endocapillary proliferation
  - Mesangial proliferation
  - Neutrophil infiltration
  - Subepithelial deposits

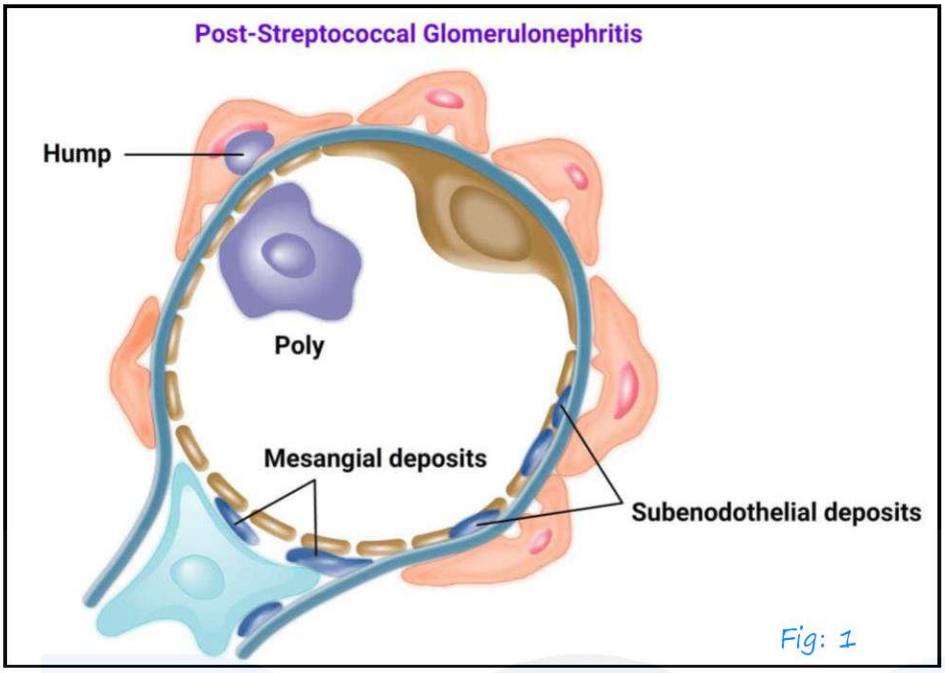

Fig: 1

Clinical features 00:13:52

- Children
  - Acute nephritis
  - Complications
    - i. Acute LVF
    - ii. Hypertensive encephalopathy
    - iii. RPGN

- Adults
  - Nephritic presentation
  - Higher chance of RPGN

Investigations

- H/o cola coloured urine⊕
  - Serum C_3 decrease → normalise by 2 months
  - Anti DNA se B increase (70% cases)

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- ASO titre increase (30% cases) → not clinically relevant

- Biopsy → light microscope

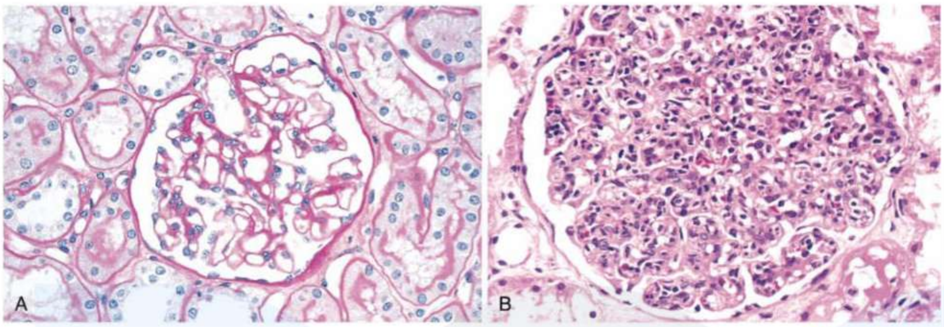
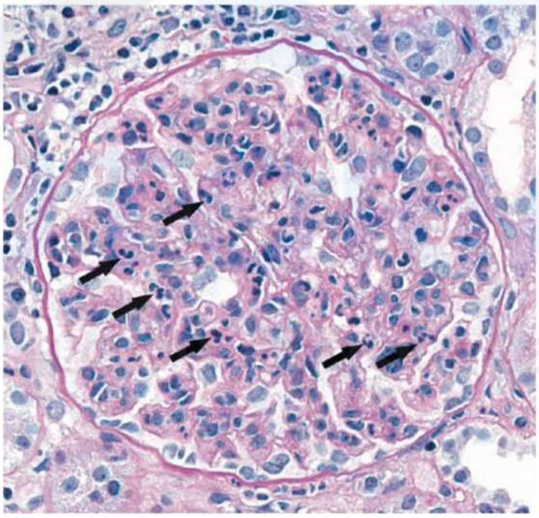


Fig: 2

- Large glomeruli
- Increased cellularity in endocapillary, mesangial



Neutrophilic infiltration Fig: 3

- Immunofluorescence

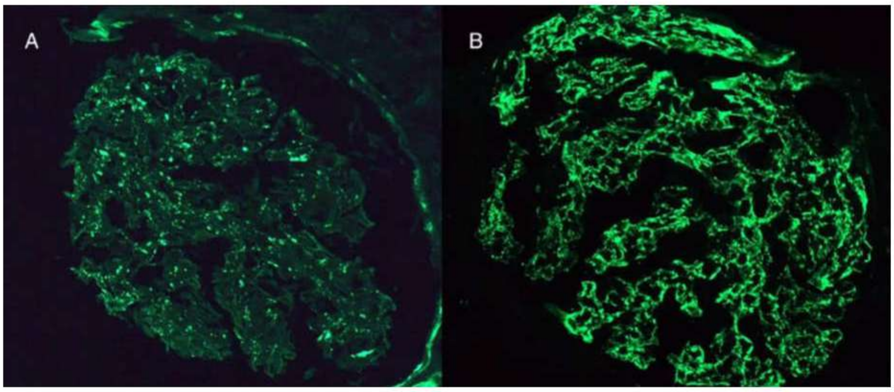


Fig: 4

- A – starry sky pattern (children)
- B – Garland pattern (adults)
- Deposits of IgG and C_3
  i. Diffuse granular → starry sky
  ii. Dense deposits → garland pattern

- Electron microscope

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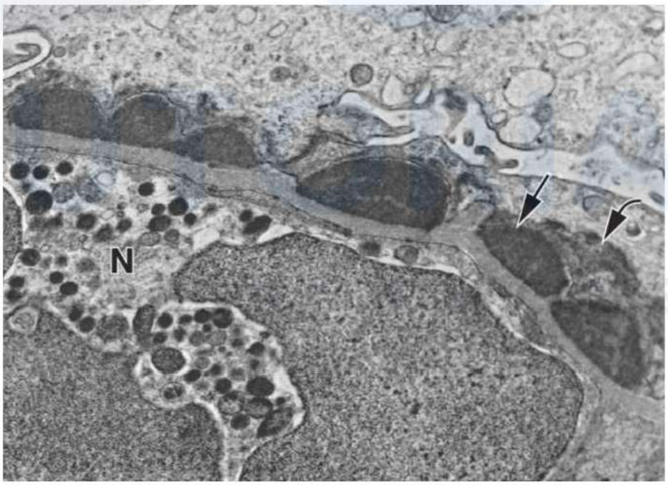

Fig: 5

- Subepithelial electron dense humps

Treatment 00:28:25

- Childhood IRGN – Good prognosis (90-95%)
  - Salt and fluid restriction

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   - BP control
- Antibiotics – controversial
   - Benzathine penicillin
- Steroids – No role

Adults

- Steroids → if it goes for rapid progressive d/s .

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RPGN & GOOD PASTEUR SYNDROME

RPGN 00:01:22

- Rapid deteriation in renal function that occurs over weeks
- Because of glomerular affection

TYPES OF RPGN

- Type 1: occurs because of anti GBM disease protype of type 1-Good Pasteur's disease
- Type 2: Because of immune complexes
  (SLE, IRG11)
- Type 3: Pauci-immune
  (ANCA associated vasculitis)
- Type 4: DOUBLE POSITIVITY
  Anti GBM positive
  ANCA Positive
- HPE: All 4 types are characterized by crescents
  ↓
  - Proliferation of epithelial cells of bowmans capsule
  - Infiltration by monocytes and macrophages

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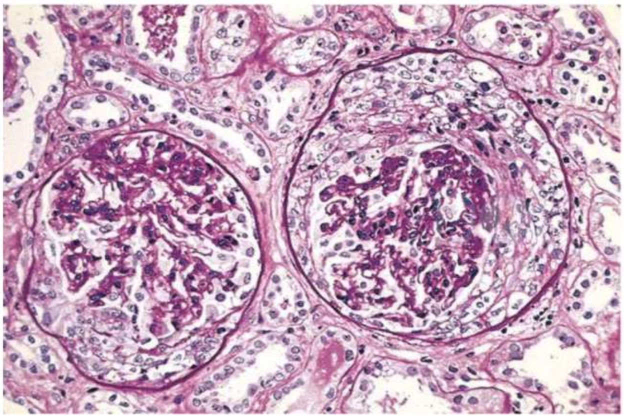

Extra capillary proliferation Fig: 1

- Also kla crescentric glomerulonephritis

  Pulmonary-renal syndrome

  - Involvement of lungs and kidney as a sequalae of disease

i. Good Pasteur syndrome

- RPGN + Alveolar hemorrhage

ii. Anti GBM disease

- Antibodies against glomerular basement membrane

iii. Good pasture disease

- Antibody against α_3 chain of non-collagenous domain of type IV collagen

Causes of lung hemorrhage and rapidly progressive glomerulonephritis

- Disease associated with antibodies to the GBM (20% – 40% of cases)
  - Good pasture disease (spontaneous anti-GBM disease)

- Disease associated with systemic vasculitis (60-80% of cases)
  - Granulomatosis with polyangiitis (Wegener) (common)
  - Microscopic polyangiitis
  - Systemic lupus erythematosus
  - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
  - IgA vasculitis (Henoch-Schonelein purpura)
  - Henoch – Schonlein purpura
  - Behcet syndrome
  - Essential mixed cryoglobulinemia
  - Rheumatoid vasculitis
  - Drugs: Penicillamine, hydralazine, propylthiouracil

Good Pasture Disease 00:20:46

- Autoimmune condition
- Characterized by IgG antibodies against α_3 chain of non-collagenous domain of type IV collagen
- Classical example of type 2 hyper sensitivity
- Bimodal age distribution → 20-30yrs → males
  60-70yrs→ males& females
- Triggering factors:
- Smokers
- Hydrocarbon exposure
- Pulmonary infection

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- Fluid overload
- Clinical manifestation:

  Pulmonary renal syndrome

  20's → pulmonary + renal involvement

  60's → renal involvement

  ↓

  RPGN

- Pulmonary involvement: cough, Hemoptysis

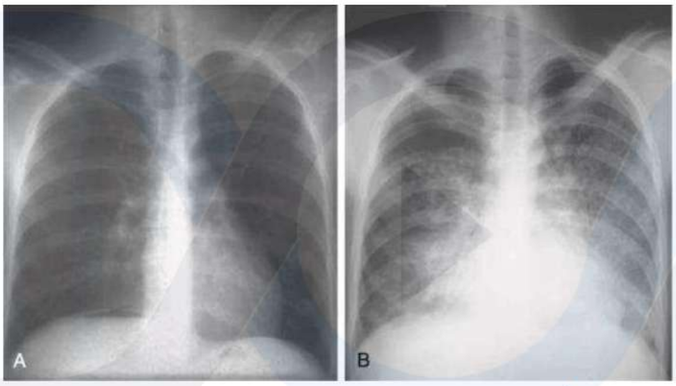

Fig: 2

- Investigations
  - Chest x ray
  - HRCT thorax
  - PFT-↑DLCO
  - Sputum→Hemosiderin laden macrophages
  - Urine examination
- Biopsy:
  - Light microscopy: crescents , areas of necrosis ,areas of glomerular sclerosis
  - Immunofluorescence:

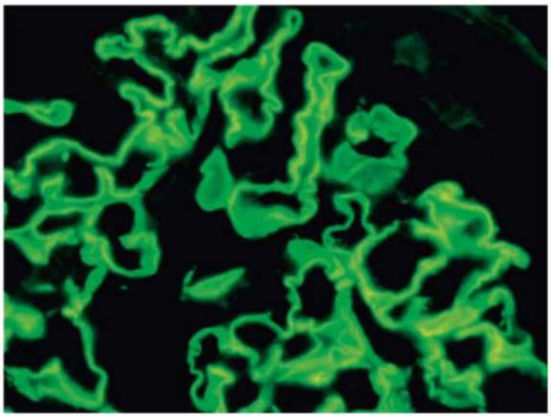

Fig: 3

Linear Ig G_3 & C_3 deposition along basement membrane

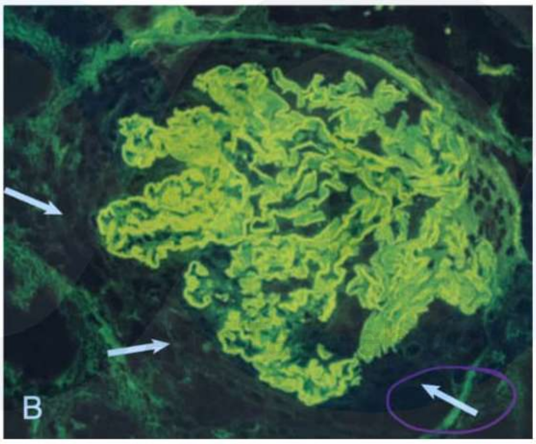

Fig: 4

- Electron microscopy:

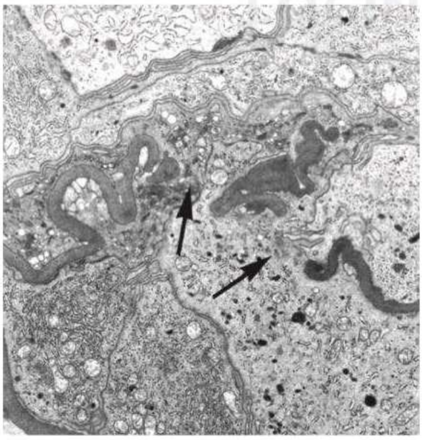

Fig: 5

Wrinkling of basement membrane focal disruptions of basement membrane

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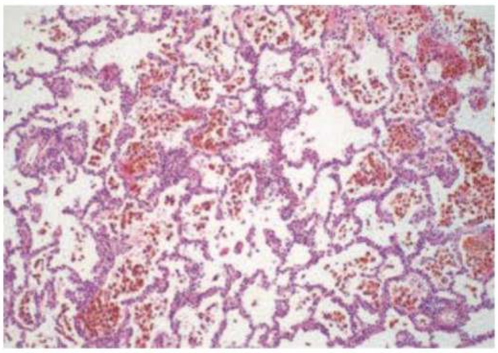

Fig: 6

- Treatment :
  - Plasma exchange + steroids + cyclophosphamide

Factors Favoring Aggressive Treatment	
Pulmonary hemorrhage	Present
Oliguria	Absent
Creatinine	<5.5 mg/dl (~ 550 μmol/l)
Other factors	Creatinine >5.5–6.5 mg/dl (~ 550 – 600 μmol/l) but - Rapid and recent progression - ANCA positive - Glomerular damage less severe than expected - Crescents recent, nonfibrous - Early renal transplantation desired

Alport Syndrome 00:00:28

Grouped under hereditary nephritis
- Alports syndrome
- Thin basement membrane disease

Alport Syndrome

- Defect in type IV collagen → component of basement membrane
- GBM
- Cochlea
- Lens
- Type IV collagen – heterotrimer – α_3, α_4, α_5 chain
- X linked 80% - m.c → Defect in α_5 chain
- Autosomal recessive (15%) → Defect in α_3/α_4 chain
- Autosomal recessive (5%)

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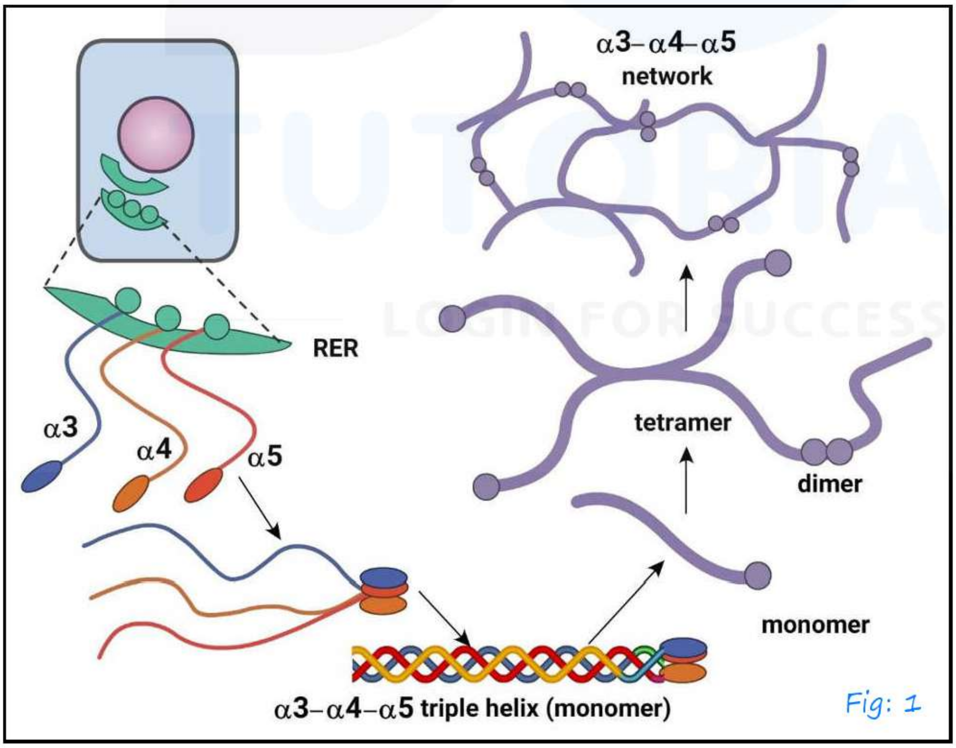

Fig: 1

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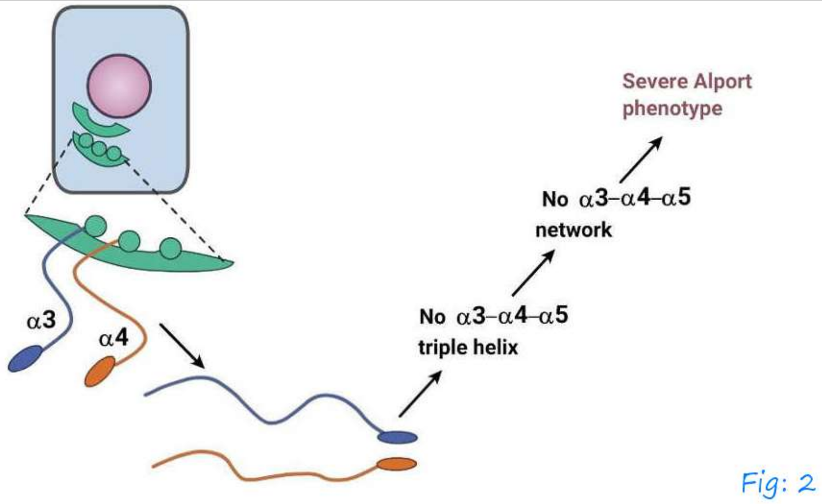

Fig: 2

Effect of a "severe" COLA4A5 mutation: deletion, frameshift, premature stop

- Defective $\alpha_3, \alpha_4, \alpha_5$ helix
- Compensatory $\alpha_1, \alpha_2, \alpha_3$ helix
- Susceptible to proteases
- Alternate thinning and thickening of BM
- Splitting and laminantion of BM
- BASKET WEAVE APPEARANCE

Clinical Feature 00:11:40

- Age:
- Manifestation in 1st decade
- Microscopic hematuria
- Episodic macrohematuria (infection, exercise)
- Obvious hematuria
- Proteinuria
- HTN
- 3rd decade – ESRD

(Obvious hematuria, Proteinuria, HTN, 3rd decade – ESRD: Occur in 2nd decade)

Extrarenal manifestations

Anterior lenticonus

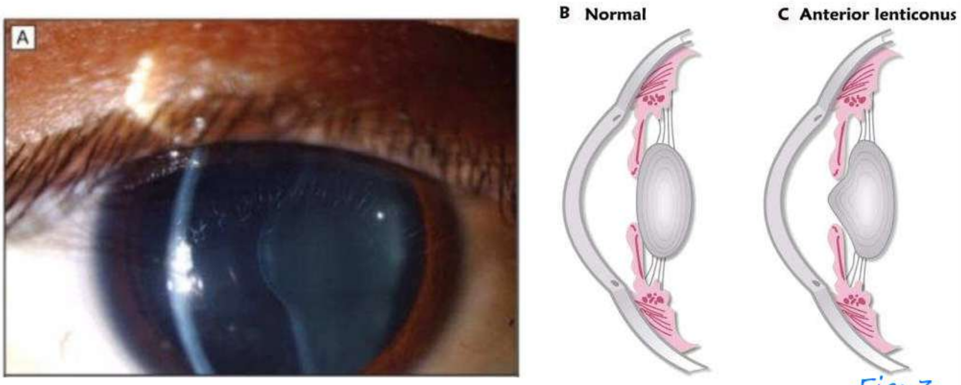

Fig: 3

Dot and fleck retinopathy

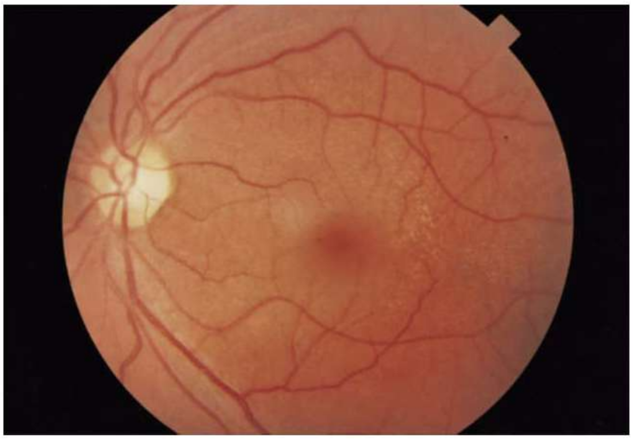

Fig: 4

- Corneal dystrophy
- SNHL
- Mental retardation
- Leimyomatosis

In x linked AS
- Males → Severe phenotype
- Females → carriers

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- AR & AD: both males and females have similar presentation

Investigations

- Biopsy
- Light microscopy: No specific changes
- Immunofluorescence

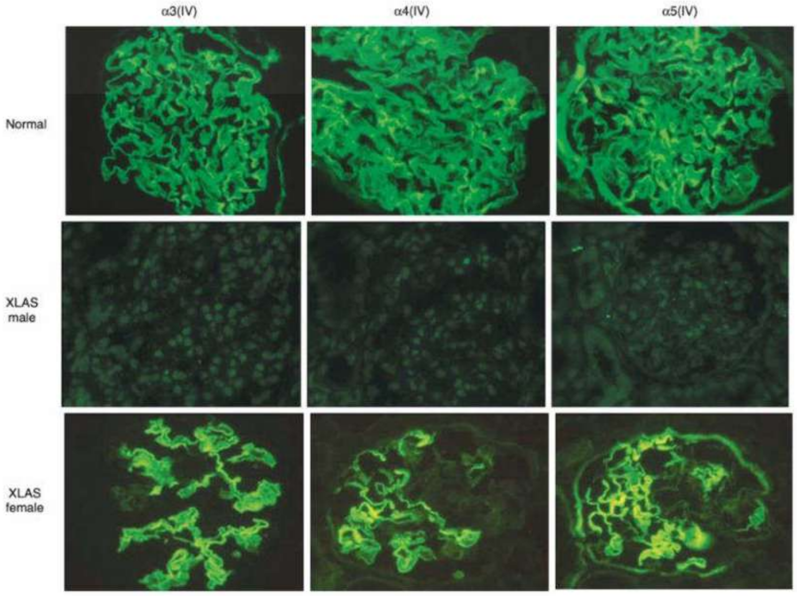

Fig: 5

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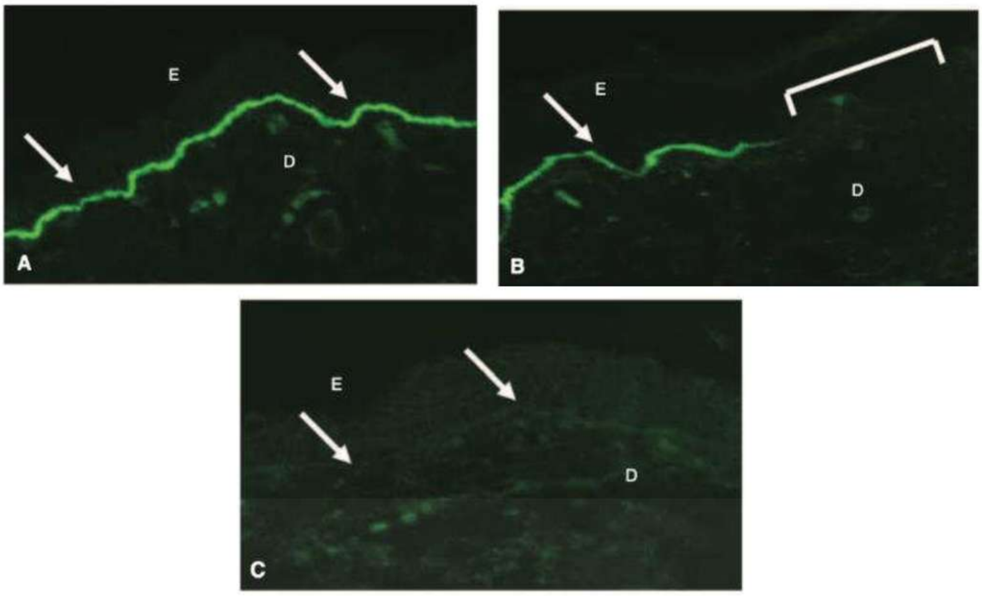

Immunofluresence of skin biopsy

Fig: 6

- Electron microscopy: Diagnostic of alport syndrome

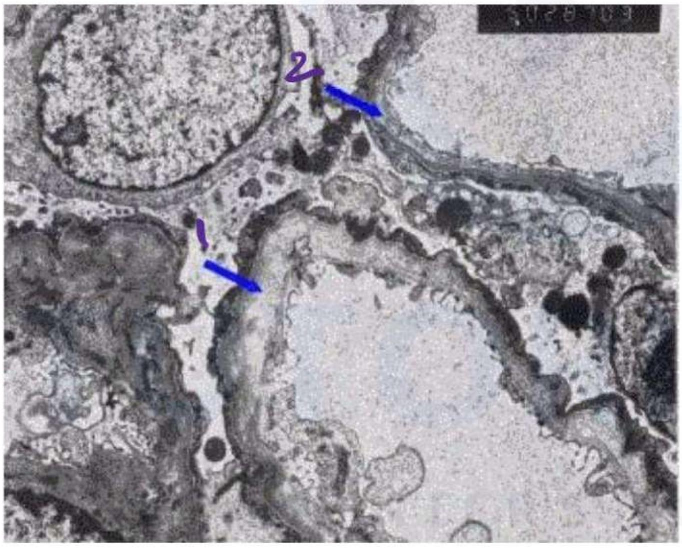

Fig: 7

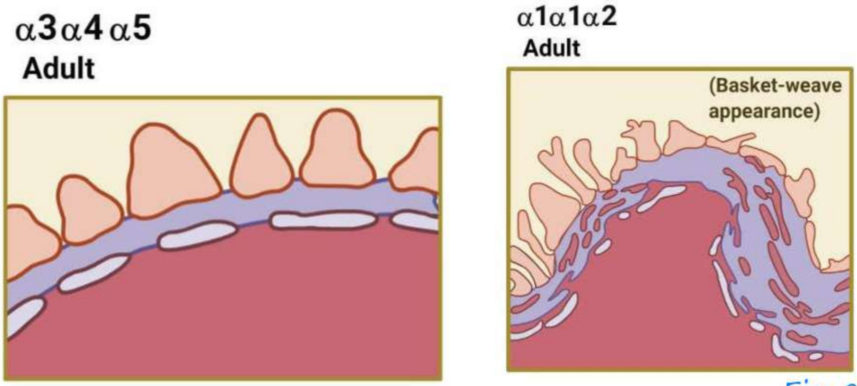

Fig: 8

Treatment

- ALE inhibitors / ARB's
- Renal transplant – definitive Rx
- Does not recur after transplant
- Defective α_3 chain
- Antibodies against α_3 chain
- Good pasture syndrome

} Post-transplant

Thin basement membrane disease

- Type IV collagen defect - α_3/ α_4 chain
- Autosomal dominant
- Uniform basement membrane thinning
- Clinical feature
  - Hematuria
  - No proteinuria
  - No HTN
  - No progression to ESRD
  - No extra renal manifestations

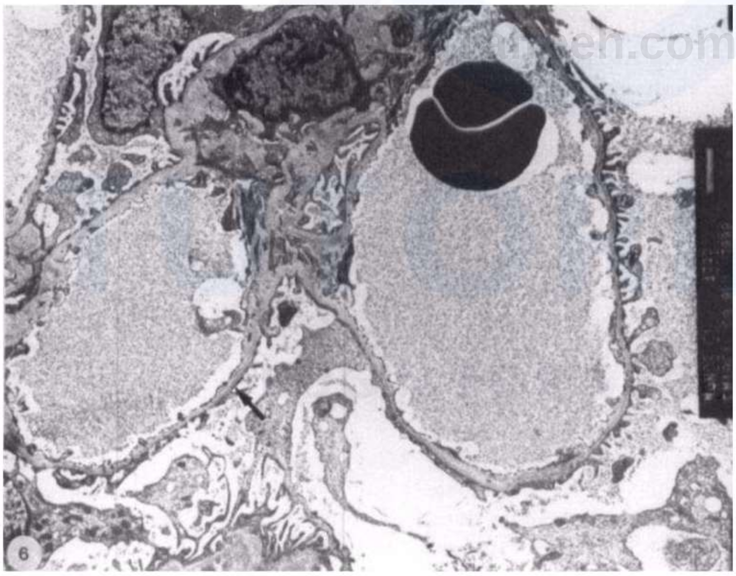

Fig: 9

Electron microscopy
↓
Uniform thinning of BM

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RENAL ARTERY STENOSIS

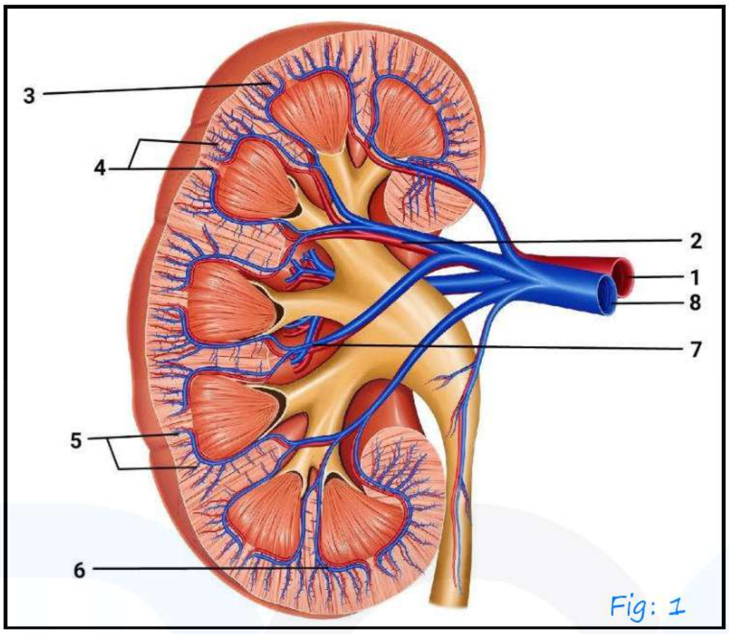

Fig: 1

1.Renal artery

2.Interlobar arteries

3.Arcuate arteries

4.Interlobular arteries

5.Interlobular veins

6.Arcuate veins

7.Interlobar veins

8.Renal vein

- Renal artery – larger caliber vessel
- Interlobar arteries
- Arcuate arteries
- Interlobular arteries

(Interlobar, arcuate and interlobular arteries) — **Smaller caliber vessel**

Renal artery stenosis 00:01:52

- Etiology
  - Most common causes in elderly – Atherosclerosis
  - Most common causes in younger
    - i. Fibromuscular dysplasia (worldwide) (FMD)
    - ii. Takayasu arteritis (India)

Characteristics of atherosclerotic renal-artery stenosis and fibromuscular dysplasia

Variable	Atherosclerosis	Fibromuscular dysplasia
Age at presentation	Older (>50years)	Usually young (<40years)
Sex	Either	Usually female
Lesion location	Ostial, proximal, middle	Middle or distal
Blood-pressure response to revascularization	Unclear	Normotension in most patients

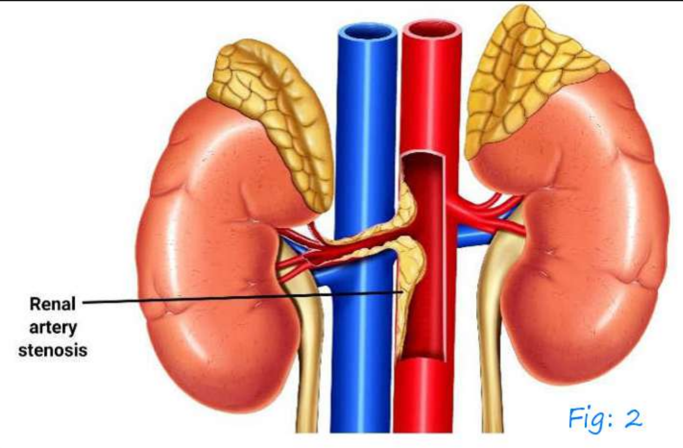

Fig: 2

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- PTRA – Percutaneous transluminal renal angioplasty
  - FMD responds better than atherosclerosis

Clinical features 00:08:30

- Depends on unilateral (or) bilateral RAS (Renal a stenosis)
- Refractory HTN (another name of RAS – Reno vascular HTN)

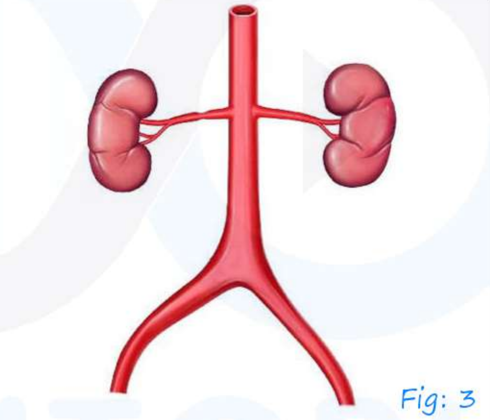

Fig: 3
Unilateral renal artery stenosis

Reduced renal perfusion

↓

Increase renin-angiotensin system (RAS)

Increase renin

Increase angiotensin II

Increase aldosterone

↓

Angiotensin II dependent hypertension

Increased renal perfusion

Supressed RAS | Increased Na^+ excretion (pressure natriuresis)

- Angiotensin II – Potent vasoconstrictor because which they would be angiotensin II dependent HTN
- No fluid overload in unilateral artery stenosis

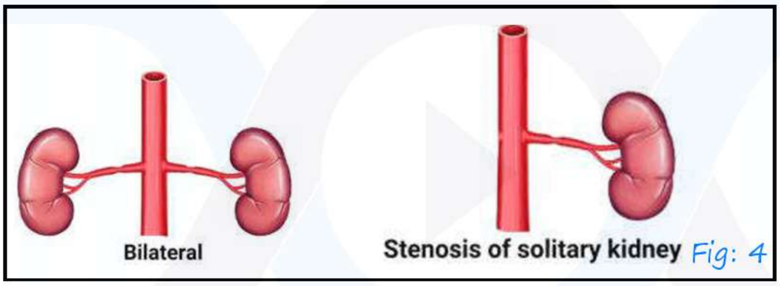

Fig: 4

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Bilateral | **Stenosis of solitary kidney**

Reduced renal perfusion

Or impaired kidney function

Increase renin - angiotensin system (RAS)
Increase renin
Increase angiotensin II
Increase aldosterone
↓
Normal or low angiotensin II

Impaired Na^+ and water excretion
↓
Volume expansion → **Inhibits RAS** (Increase renin)
↓
Increased arterial pressure

- May present as acute pulmonary edema (due to fluid overload) (fluid pulmonary edema)

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Unilateral	Bilateral
HTN No fluid overloads No flash pulmonary edema RFT – Normal Urine output – Normal USG: unilateral shrunken kidney	HTN Fluid overload Pulmonary edema RFT – Impaired Urine output–Decreased USG – Bilateral decreased renal size

- ACE I/ARBs C/I in Bilateral RAS because
- Angiotensin II is producing efferent arteriolar constriction. So, it is important to maintain a normal filtration pressure across glomerulus
- So, we can give ACE – what happens is the – efferent arteriole will be dilated, decreases the perfusion pressure

Investigations 00:22:15

- Screening method: USG kidney

+

Renal artery doppler

↓

Increase peak systolic velocity

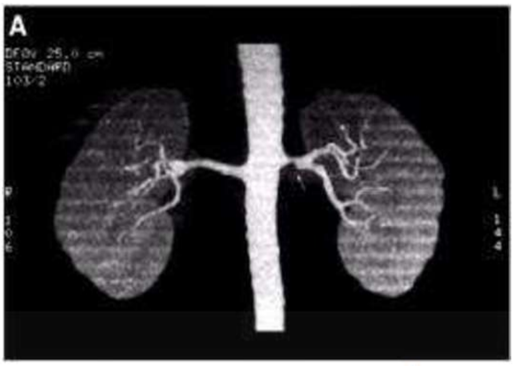
Increase resistivity index

- Ischemia resulting in renal damage – Ischemic and nephropathy

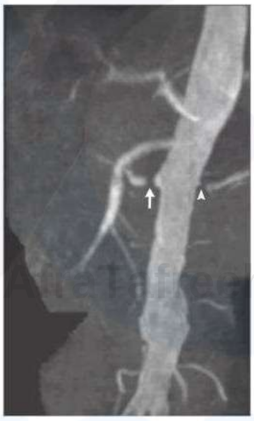
↓

O/E – Bruit ⊕ ← due to atherosclerosis

- IOC: CT angiogram
  - MR angiogram → sometimes may overestimate the stenosis



CTA Fig: 5



MRA Fig: 6

- Gold standard – DSA (Digital subtraction angiography)

DSA – Left renal artery stenosis Fig: 7

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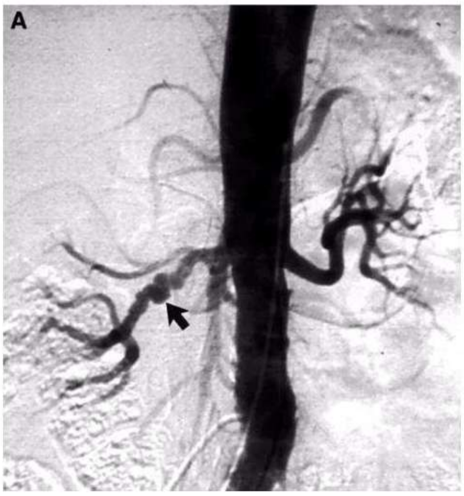

DSA – string of beads appearance
↓
FMD

Fig: 8

- Most common histologic subtype of FMD – Medial fibro-dysplasia
  - Captopril enhanced renography → Radionuclide scan
  - Captopril DTPA scan

Treatment

Medical management | Endovascular → PTRA

Endovascular procedure

- Bilaterality
- Progression
- Higher degree of stenosis
- FMD

Medical

- Unilateral – ACET/ARB's
- Antiplatelets
- Statins

ARPKD

- Autosomal recessive polycystic kidney disease
- Less common than ADPKD
- Autosomal recessive

Genetics 00:01:17

- Ciliopathy
- $PKHD_1$ gene
  i. Chromosome 6p
  ii. Codes for protein fibrocystin (polyductin)

Gross specimen Fig: 1

- Lesser number of cysts
- Cysts are smaller
- Predominantly medullary cysts (cortical cysts also)
- Radial cortical striations

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Clinical features 00:06:28

- Perinatal presentation
- Neonatal
- Infantile
- Juvenile

- Fetal USG – as early as 24 weeks → cysts in kidney
  - Echogenic kidney medullary > cortical loss of CMD
  - Development of oligohydramnios
- Perinatal presentation neonatal → most common causes of death → pulmonary insufficiency

- Infantile ⎤
- Juvenile ⎦ – More of renal problems
  ↓
  - Hypertension
  - Renal insufficiency
  - FSRD

- Hepatic manifestations
  - Congenital hepatic fibrosis
  - Defect in biliary system

↓

Intrahepatic biliary dilatation

↓

Carolis d/s

- Hepatic fibrosis can lead on to
  - Portal hypertension
  - Hematemesis

Evaluation 00:13:59

- Antinatal – Fetal USG
- CT/MRI – Abdomen

Treatment

- Control HTN – ACE inhibitors
  - ARBS
- ESRD
  - Dialysis
  - Renal transplantation
- Hepatic symptoms are dominates – hepatic transplantation
- Portal HTN ⊕ → portosystemic shunt.

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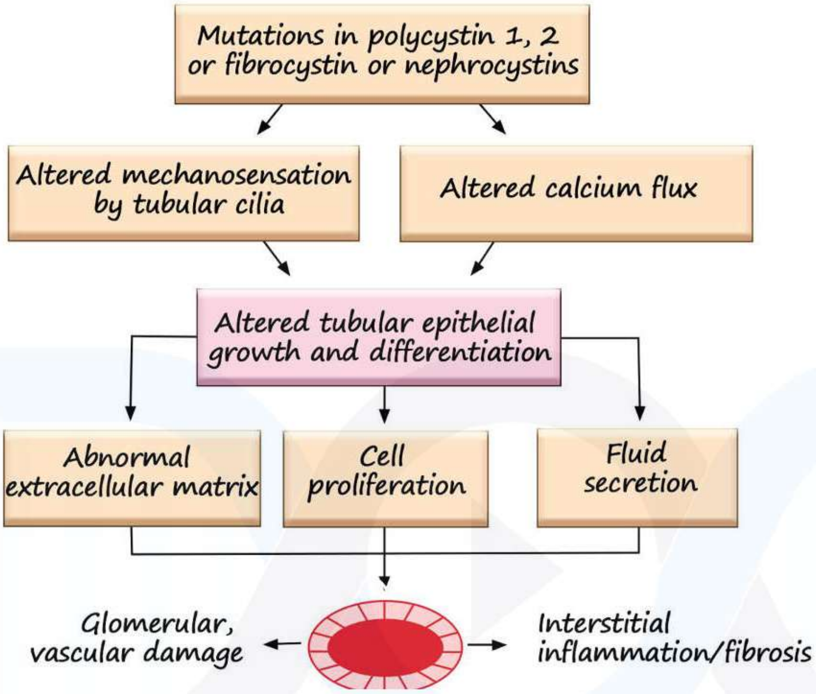
ADPKD

ADPKD 00:01:33



- Cilia is important for differentiation of tubular epithelial cells

ADPKD 00:05:30

- Autosomal dominant polycystic kidney disease
- Autosomal dominant
- Characterised by multiple epithelial lined cysts

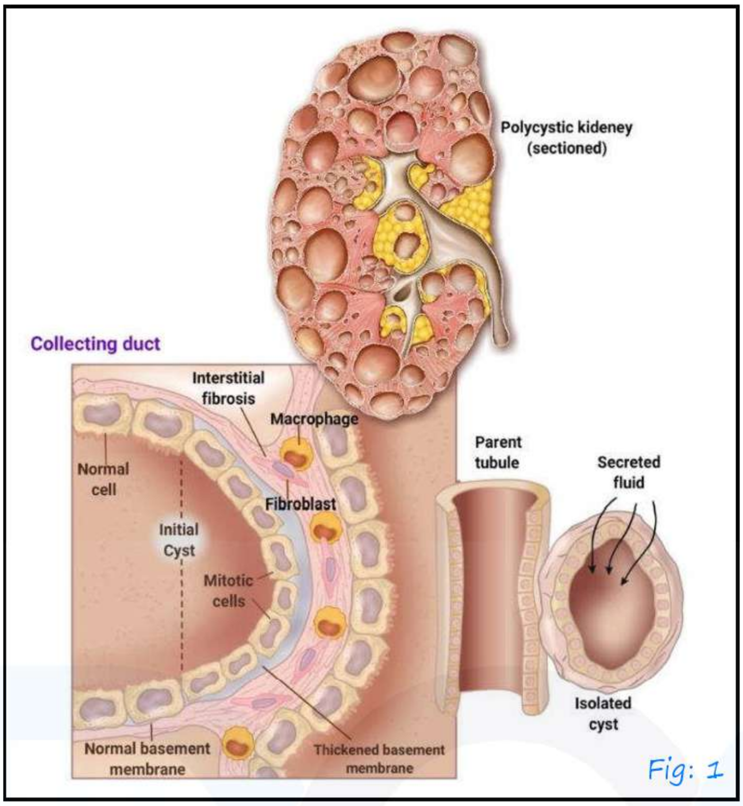


Fig: 1

- Enlarged kidney C cortical cysts & medullary
- Corticomedullary differentiation (CMD) lost in ADPKD

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Genetics 00:08:10

- AD with good penetrance and variable expressivity
- Genes
- pkD1→ codes for pc_1 (polycystin-1)- chr.16p (m/c)
- pkD_2 → codes for pc_2 (polycystin-2)- chr.4q
- Can be called ciliopathies

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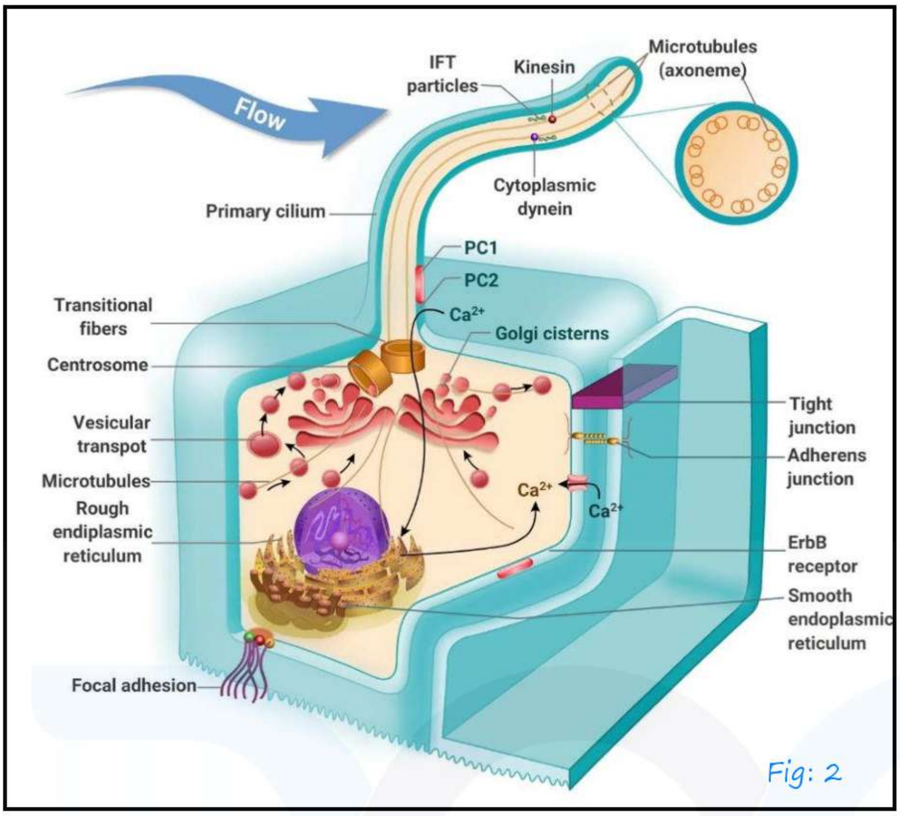

Fig: 2

Clinical Features 00:12:50

- Age: 30-50 years
- Asymptomatic
- Renal cyst → B/L
- 3rd decade of life – cyst in one kidney
- Renomegaly
- Only 5% of tubules undergo cyst formation

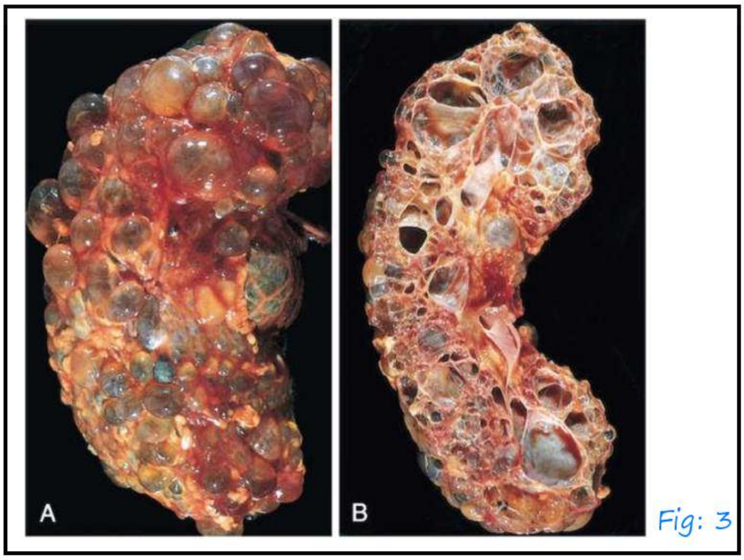

Fig: 3

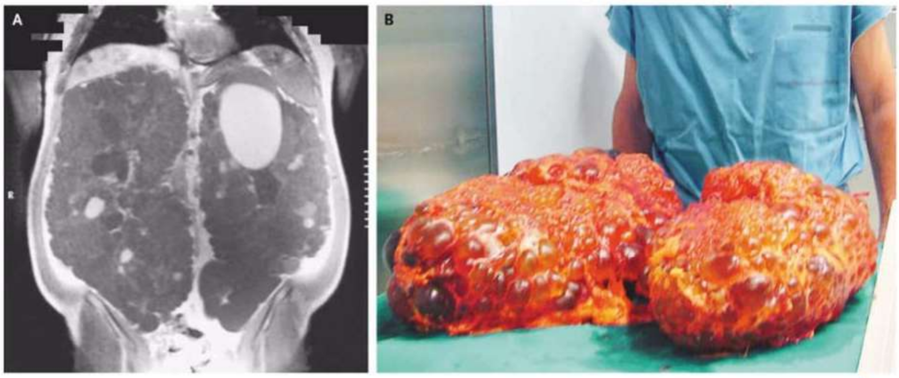

Fig: 4

- Common – back pain
- Common – flank pain
- These cysts can undergo infection → UTI

  → pyelonephritis
- Cyst rupture → hemorrhage
- Hemoglobin in cyst → hemosiderin
- Urinary calculi/nephrolithiasis

  ↓
- m/c – uric acid stone
- 2nd m/c – calcium oxalate stone
- No increased risk of RCC
- If ADPKD patient develops RCC → bilateral, multifocal
- HTN – increases renin angiotensin aldosterone system
- Increase sympathetic activity

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Renal Manifestations of Autosomal Dominant Polycystic Kidney Disease

- Functional Manifestations
  - Concentrating defect
  - Reduced renal blood flow
- Hypertension → Target organ damage
  - Cardiac
  - Cerebrovascular
  - Arteriolosclerosis and glomerulosclerosis
  - Peripheral vascular disease
- Pain, caused by
  - Cyst hemorrhage
  - Gross hematuria
  - Nephrolithiasis
  - Infection
  - Renal enlargement
- Reduced Glomerular filtration rate, possible caused by
  - Interstitial inflammation
  - Apoptosis of tubular epithelial cells
  - Hypertensive glomerulosclerosis
  - Compression atrophy

Extrarenal manifestations

- M/c – hepatic cyst → single large cyst
- Multiple moderate to large
- Multiple small cysts

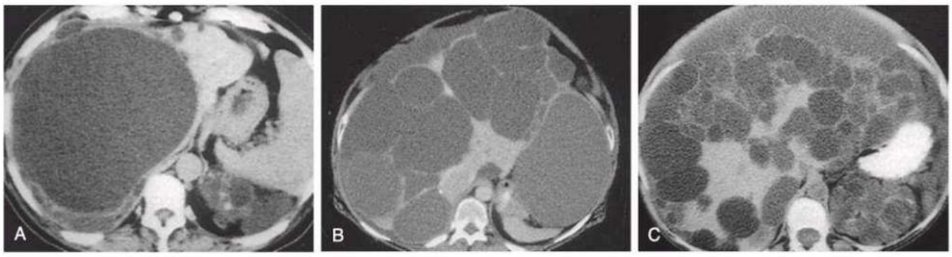

Fig: 6

- Colonic diverticula
- Abdominal wall hernia
- Cysts in pancreas, seminal vescicles, spleen
- Arachnoid cyst
- Intracranial aneurysms → berry/saccular aneurysm
- Tunica media

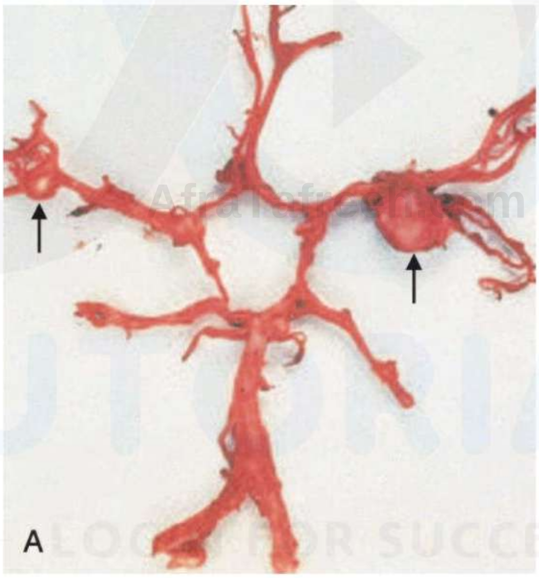

Fig: 7

Intracranial aneurysms
- Asymptomatic
- Symptomatic
  - Unruptured
  - Ruptured

- Strokes
- Dolicoectasias
- Arterial dissection

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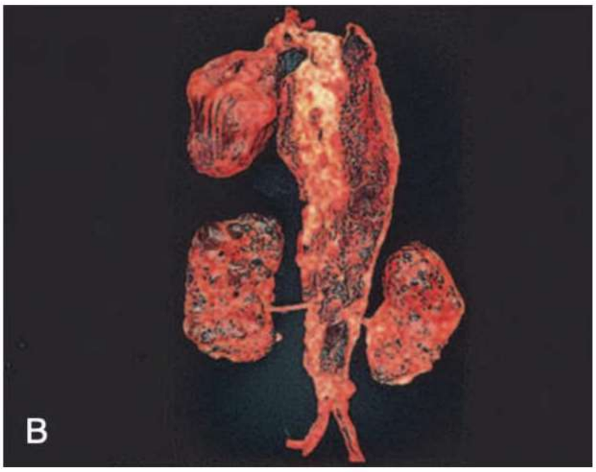

Thoracic and abdominal aorta dissection Fig: 8

- CVS manifestations

  a. Mitral valve prolapses (30%)

  b. MR

  c. AR

Evaluation: 00:38:10

- USG
- CT/MRI abdomen
- Echo
- Barium enema
- ECH – L ventricular hypertrophy

(USG, CT/MRI abdomen, Echo — Cyst)

Ultrasound Criteria for the diagnosis of autosomal dominant polycystic kidney disease

Ultrasound criteria for the diagnosis of autosomal dominant polycystic kidney disease			
Age (y)	Criteria	PPV	NPV
Original Ravine's PKD 1 diagnostic criteria			
15-29	≥ 2 cysts, unilateral or bilateral	99	88
30-39	≥ 2 cysts in each kidney	100	88
40-59	≥ 2 cysts in each kidney	100	95
≥ 60	≥ 4 cysts in each kidney	100	100
Revised unified diagnostic criteria			
15-29	≥ 3 cysts, unilateral or bilateral	100	86
30-39	≥ 3 cysts, unilateral or bilateral	100	86
40-59	≥ 2 cysts in each kidney	100	95
≥ 60	≥ 4 cysts in each kidney	100	100

Treatment 00:44:00

i. HTN → AE I/APBs → hyperkalemia → K^+ binding resins

- Target BP: 130/80 mmHg
- Young: 110/75
- Otherwise, healthy

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1.Infections:

Antibiotics that penetrate cyst wall

- Chloramphenicol
- Quinolones
- Cotrimoxazole

2.Renal calculi

3.Hemodialysis or peritoneal dialysis

4.Renal transplantation

- Indications for pretransplant native nephrectomy in patients with ADPKD.
  1.Huge kidney size causing insufficient space for graft placement.
  2.Recurrent cyst infection or bleeding.
  3.Symptomatic and recurrent stones.
  4.Chronic pain (reducing QOL or requiring narcotics)
  5.Pressure symptoms (early satiety, repeated vomiting)
  6.Suspected malignancy.

5.Newer agents → Tolvaptan, Octreotide } Decreases CAMP levels

CAMP is required for cystogenesis

- MTOR inhibitors (mammalian target of rapamycin)

↓

Everolimus

sirolimus

NEPHRONOPHTHISIS & ADTKD

- ADTKD – Autosomal dominant tubule interstitial kidney disease
- Both these disorders (Nephronophthisis & ADTKD) are characterized by similar HPE findings
  i. Tubular cysts
  ii. Tubular basement membrane irregularities
  iii. Tubule interstitial cell infiltration with fibrosis
- Both these disorders are characterized by cyst formation in corticomedullary junction

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Nephronophthisis 00:03:33

- >90 genes involved
- Predominant genes
  - NPHP 1-20
  - Code for protein nephrocystin
- Autosomal recessive

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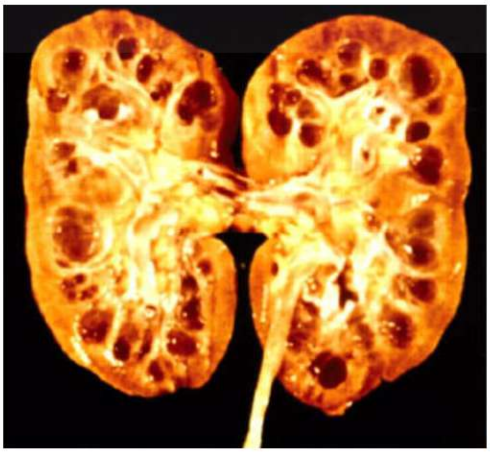

Fig: 1

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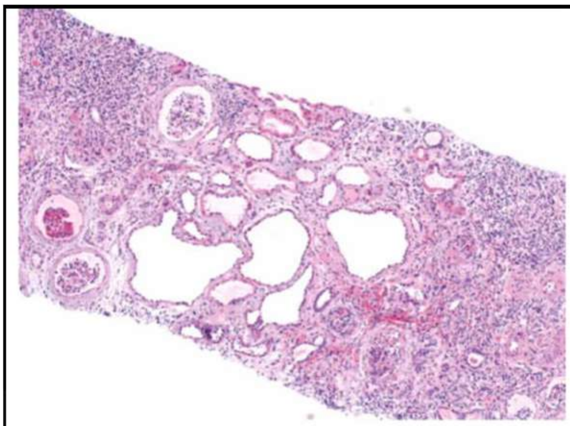
- Gross – bilateral cysts @ corticomedullar junction



HPE Fig: 2

Clinical features

- INFANTILE
- JUVENILE -mc
- ADOLOSCENT
- Manifestations begin @ 4-6years
- Polyuria, salt losing, growth retardation, skeletal abnormalities → renal rickets
- Average age of developing end stage renal disease
- ESPD – 13 years
- Can also have extrarenal manifestations

NDHP + Retinitis pigmentosa → senior loken syndrome

-

NPHP + cerebellar vermis aplasia → joubert syndrome

Fig: 3

Molar tooth sign

↓

Joubert syndrome

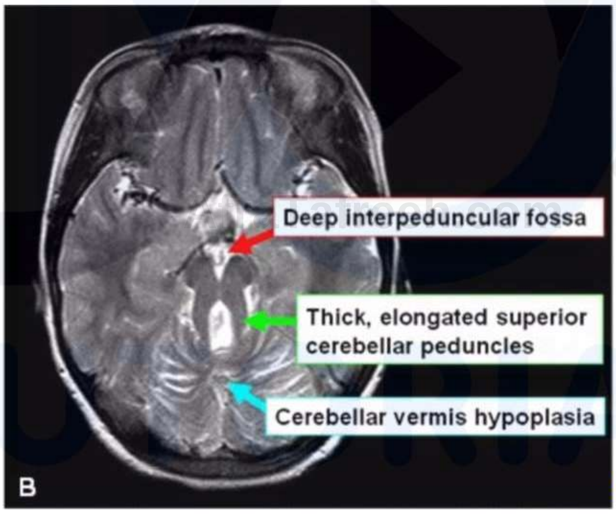


Fig: 4

- NPHP like illness + obesity + polydactyly + Retinitis pigmentosa → Bardet – Biedel syndrome

Treatment

- Dialysis
- Renal transplant

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ADTKD 00:13:00

- AD
- HPE same
- Age of onset → 3rd decade
- Patient develops ESRD by 4th–5th decade
- Previously referred to as medullary cystic kidney disease (MCKD)
- 2 types
  i. MCKD 1→ MUC1 gene (MUCIN1)
  ii. MCKD 2 → UMUD gene (uromodulin)
- Clinical features
  - Same as NPHD
  - No skeletal abnormalities
- Extra-renal manifestations
  - Hyperuricemia
  - Gout
- Treatment
  - Dialysis
  - Renal transplant

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TUBEROUS SCLEROSIS & VHL SYNDROME

Tuberous sclerosis 00:01:11

- AD
- Neurocutaneous syndrome
- Bournville's disease

Genetics

- AD
- 2 genes
  - i. TSC_1 gene → chromosome 9q → Hamarin
  - ii. TSC_2 gene → chromosome 16p → Tuberin
- Normal individuals → hamartin and tuberin complex

↓

Inhibit m TOR pathways

M-tor → for cell proliferation pathway

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Renal manifestations

i. Renal angiomyolipomas

ii. Renal cysts

iii. Renal cell carcinoma

- Renal angiomyolipomas
  - Most common renal manifestation
  - Vascular + smooth m/s + fat component

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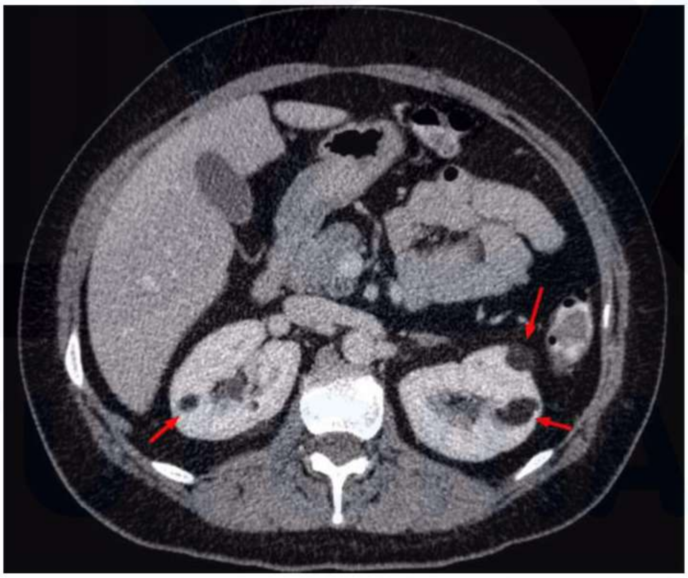
Gross section Fig: 1



CT image → multiple bilateral angiomyolipomas Fig: 2

- Totally asymptomatic
- Chance of bleeding into subcapsular and peri-rental space
  - Flank pain
  - Flank mass
  - Hypotension

  (Flank pain, Flank mass, Hypotension → Wunderlich syndrome)
- Renal cysts
  - Larger ADPKD
  - Can turn malignant

Other manifestations

- Dermatological
  - Ash leaf macules
  - Adenoma sebacium
  - Shagreen patches → lumbosacral area
  - Periungual fibromas (koenen tumors)
- Neurological
  - Epilepsy
  - Vogt's triad
    i. Epitespy
    ii. Low intelligence
    iii. Adenoma sebacium
  - Cortical tubers ⊕ → lesions in CNS
  - SEGCA (Subependymal Giant Cell Astrocytomas)

Candle wax appearance:

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Fig: 3

- Retinal
  - Retinal astrocytomas
  - Multinodular cysts – retina, optic disc
- Cardiac – Rhabdomyoma

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Major

- Facial angiofibromas or forehead plaque
- Nontraumatic ungual or periungual
- Hypomelanotic macules (>3)
- Shagreen patch (connective tissue nevus)
- Multiple retinal nodular hamartomas
- Cortical tuber(s)
- Subependymal nodule
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyoma(s) (≥1)
- Lymphangioleiomyomatosis
- Renal angiomyolipoma

Minor

- Multiple, random dental pits
- Hamartomatous gastrointestinal or rectal polyps
- Bone cysts
- White matter radial migration lines
- Gingival fibromas
- Nonrenal hamartoma
- Retinal achromic patch
- "Confetti" skin lesions
- Multiple renal cysts
  - Definitive tuberous sclerosis → 2 major criteria (or) 1 major + 2 minor criteria

Von-Hippel Lindau syndrome 00:17:13

- VHL gene – mutation on chromosome 3P
  - Tumor suppressor gens
    i. Renal cysts

ii. Renal cells Ca

iii. Pheochromocytoma

iv. Pancreatic cysts

v. Retinal & cerebellar hemangioblastoma

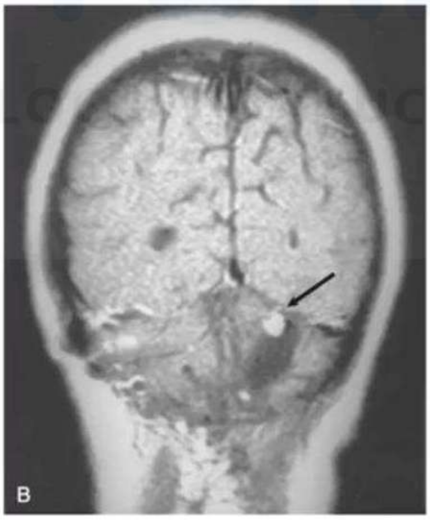
vi. Endolymphatic sac tumors

Fig: 4

Bilateral renal cysts

+

Pancreatic cysts



Cerebellar hemangioblastomas Fig: 5

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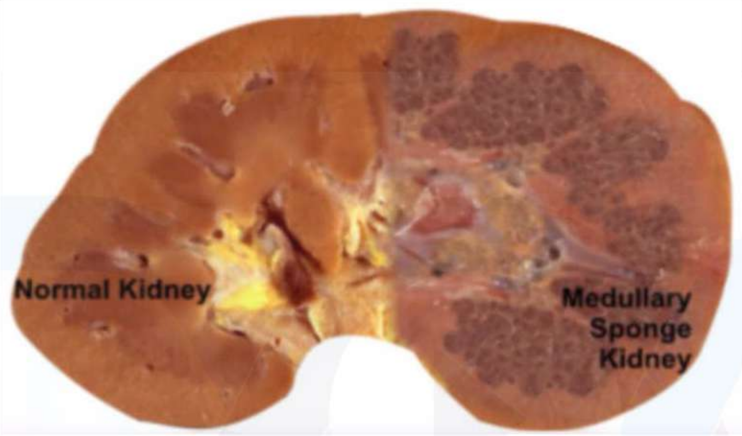
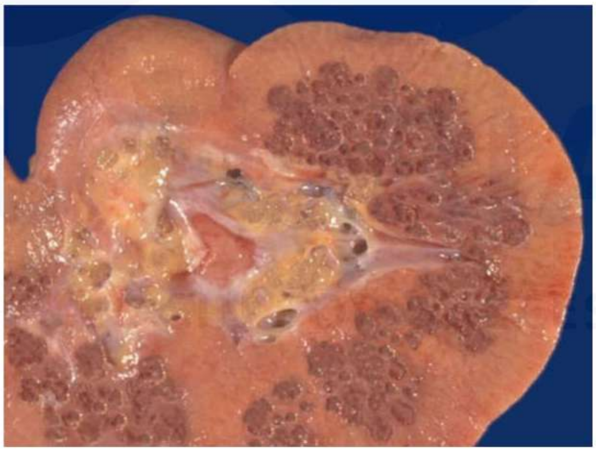
MEDULLARY SPONGE KIDNEY

- Mostly sporadic
- Characterised by dilatation of medullary collecting duct and papillary collecting duct → sponge kidney



Gross Fig: 1



MSK Fig: 2

Clinical features

- Age group: 4th–5th decade
- Manifestations : predominantly of nephrolithiasis
- Haematuria
- UTI's

- Hypercalciuria → Nephrocalcinosis
- Defective distal tubular acidification of urine
- Subgroup of patients may be asymptomatic

Treatment

- Asymptomatic – No treatment
- Focal & segmental ectasia – partial nephrectomy
- Bilateral affected → medical management
  - Potassium citrate
  - Plenty of oral fluids

Diagnosis 00:07:25

- IVP
- CT urography

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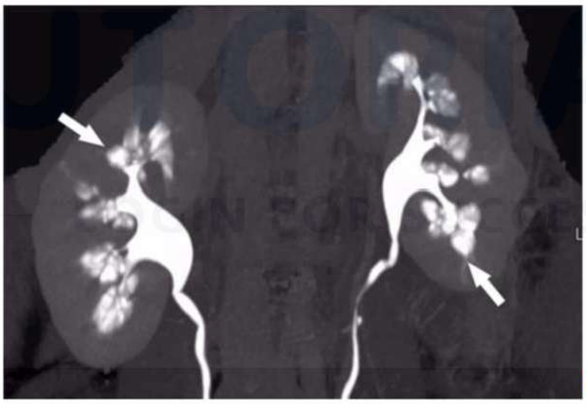

Fig: 3

- CT urography – Bouquet of flowers/paint brush appearance

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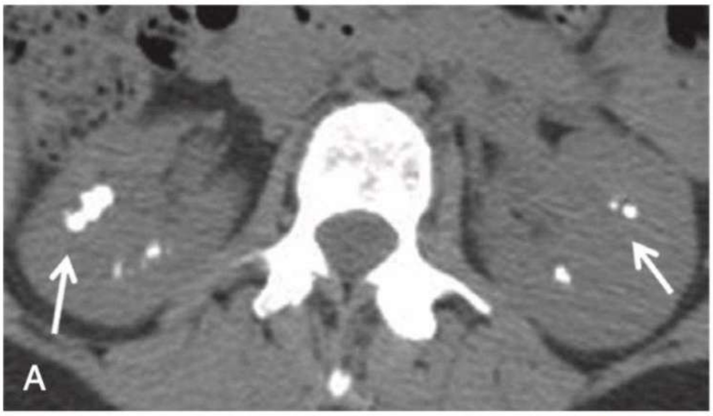

Nephrocalcinosis Fig: 4

- Stones associated with MSK are predominantly calcium phosphate stones
- Some individuals may have calcium oxalate stones

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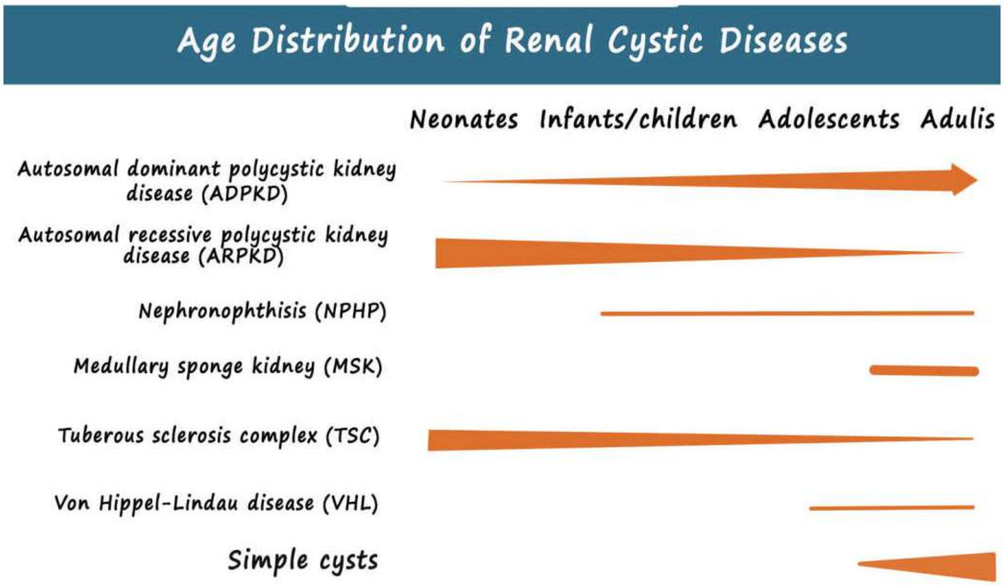

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ANTIPHOSPHOLIPID ANTIBODY SYNDROME (APLA SYNDROME)

Introduction 00:00:22

- Autoimmune disease (F>M) 9:1 ration
- Acquired thrombophilia
  - Arterial thrombosis
  - Venous thrombosis
  - Pregnancy morbidity

Pathogenesis

- Antibodies against phospholipids

  Antibodies against certain protein bound to Phospholipid like – Beta 2 glycoprotein

  – Prothrombin

  ↓

  Predisposition to develop thrombosis

Predominant antibodies 00:03:56

Name	Assay for their detection
Antibodies against cardiolipin (aCL)	Enzyme-linked immunosorbent assay (ELISA) using as antigen cardiolipin (CL), a negatively charged phospholipid

Antibodies against β2GPI (anti- β2GPI)	Elisa using as antigen affinity purified or recombinant β2GPI in the absence of PL
Lupus anticoagulant (LA)	Activated partial thromboplastin time (aPTT) Kaolin clotting time

- SLE patients – 1/3rd antiphospholipid antibody

Types 00:05:40

3 types

Primary APLA	Secondary APLA
↓	↓
- Without any particular underlying cause - Also k/a hughes syndrome	2° to a disease like - SLE (most common) - Lymphomas

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Catastrophic APLA

- Thrombosis involving 3 or more organs, organ system or tissues over a period of 1 week.

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Clinical features 00:07:57

Manifestation	%
Venous Thrombosis and Related Consequences	
Deep vein thrombosis	39
Livedo reticularis	24
Pulmonary embolism	14
Superficial thrombophlebitis	12
Thrombosis in various other sites	11
Arterial Thrombosis and Related Consequences	
Stroke	20
Cardiac valve thickening/dysfunction and/or Libman-sacks vegetations	14
Transient ischemic attack	11
Myocardial ischemia (infarction or angina) and coronary bypass graft thrombosis	10
Leg ulcers and/or digital gangrene	9
Arterial thrombosis in the extremities	7
Retinal artery thrombosis/amaurosis fugax	7
Ischemia of visceral organs or avascular necrosis of bone multi-infarct dementia	6

lacy like network – livedo reticularis Fig: 1

- Patients with APLA have accelerated risk of atherosclerosis
- Most common mortality for long standing SLE – coronary artery disease
- Most common mortality for early stage of SLE – Infection
- Fulminant presentation of SLE leading to mortality Lupus nephritis

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Neurologic manifestation of Uncertain Etiology	
Migraine	20
Epilepsy	7
Chorea	1
Cerebellar ataxia	1
Transverse myelopathy	0.5

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Renal manifestations due to various reasons (Renal artery/Renal vein/Glomerular Thrombosis, Fibrous Intima hyperplasia)	
Musculoskeletal Manifestations	
Arthralgia's	39
Arthritis	27
Obstetric manifestations (Referred to the number of pregnancies)	
Preeclampsia	10
Eclampsia	4
Fetal Manifestations (Referred to the number of pregnancies)	
Early fetal loss (<10 weeks)	35
Late fetal loss ($\geq$ 10 weeks)	17
Premature birth among the live birth	11
Hematologic Manifestations	
Thrombocytopenia	30
Autoimmune hemolytic anemia	10

Modified Sapporo criteria 00:15:24

Clinical criteria

i. Vascular thrombosis
   - One or more clinical episodes or arterial, venous, or small vessel thrombosis in any tissue or organ.

ii. Pregnancy morbidity

a. One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, or
b. One or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, severe pre-eclampsia or recognized features of placental insufficiency or
c. Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded

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Laboratory criteria

i. Lupus anti-coagulant present in plasma on two or more occasions at least 12 weeks apart, detected according to the guidelines of the international society and thrombosis and hemostasis
ii. Anti-cardiolipin antibody of immunoglobulin (Ig)G or IgM isotype in serum or plasma, present in medium or high titer (>40 GPL or MPL, or > 99th percentile), on two or more occasions at least 12 weeks apart, measured by a standardized ELISA

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iii. Anti-β_2-glycoprotein I antibody of IgG or IgM isotype in serum or plasma (in titer > 99th percentile) present on two or more occasions at least 12 weeks apart, measured by a standardized ELISA.

- If patient has got M.I and has got positive β_2 glycoprotein

↓

Repeat test after 12 weeks → positive

↓

APLA

Treatment 00:20:12

- Totally asymptomatic, incidentally found aPTT increases

↓

No treatment

- If individual is developing a thrombotic episode (arterial or venous) → anticoagulation

↓

Acute stages – LMWH/Heparin + warfarin in initial stages (3-5 days)

↓

Once warfarin reaches therapeutic range – continue with warfarin lifelong

- Target INR – 2-3

- Recurrent thrombosis → LMWH/Heparin + Warfarin

↓

once warfarin reaches therapeutic range –

continue with warfarin lifelong

- Target INR 3-4

Consider adding low dose aspirin – 81 mg (75mg)

- Pregnant female → LMWH through out pregnancy

Post partum – warfarin

Life long anticoagulant

Consider adding low dose aspirin.

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SYSTEMIC SCLEROSIS

Scleroderma 00:00:48

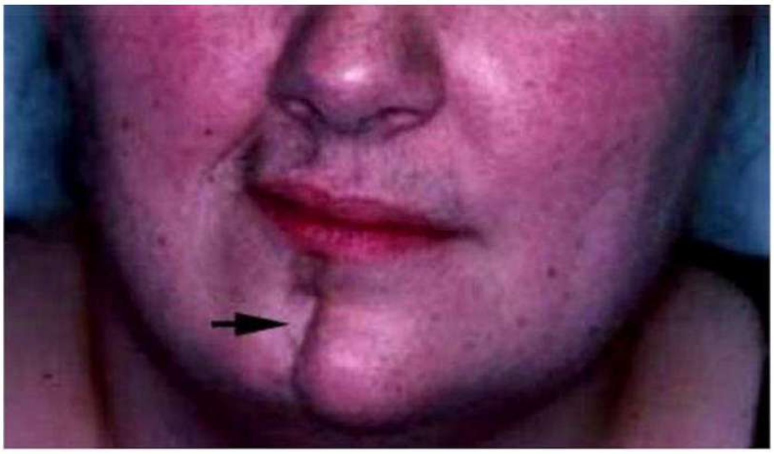
- Scleroderma – Thickening of skin
- Divided into 2 forms

2 forms

Localized	**Generalized**
↓	↓
Morphia	Limited cutaneous systemic sclerosis
Linear scleroderma	Diffuse cutaneous systemic sclerosis

Fig: 1

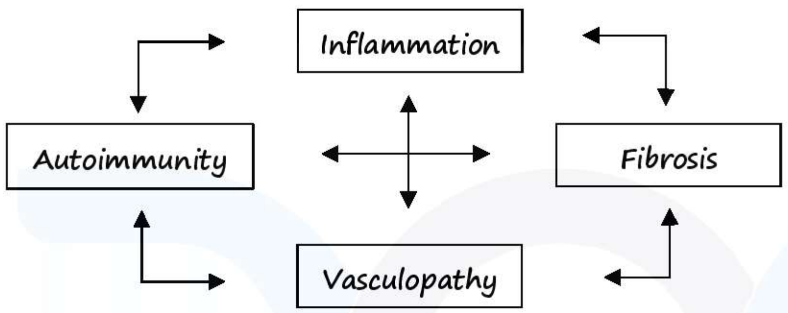
Morphea-patches of dicrete skin thickening



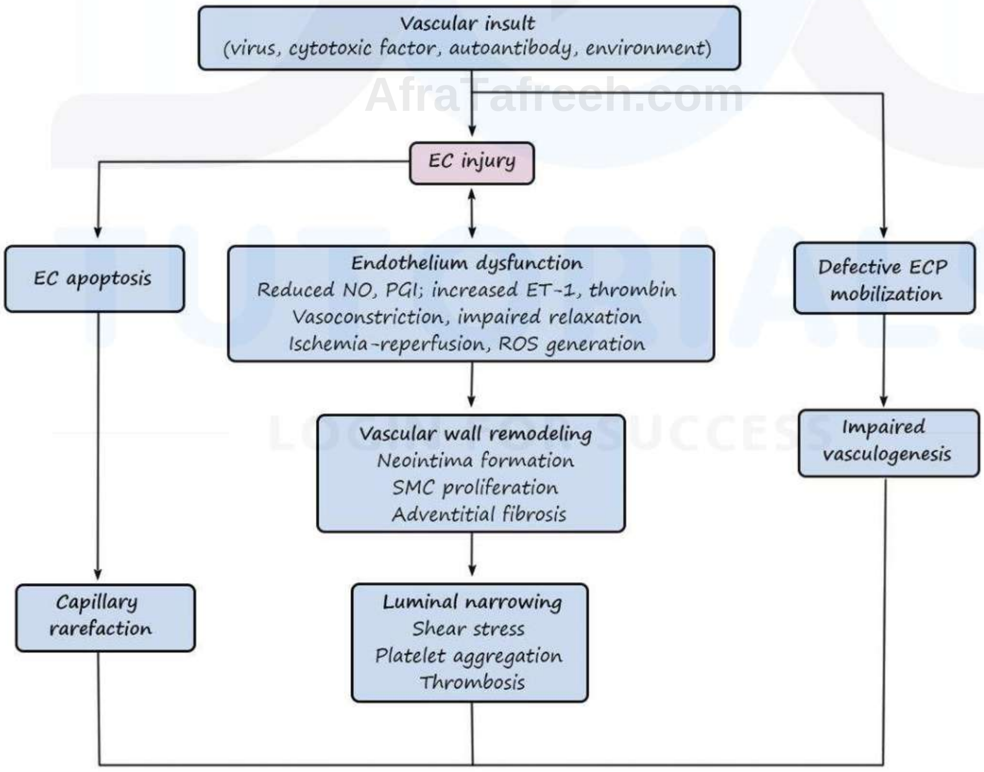
Linear scleroderma Fig: 2

Systemic sclerosis 00:04:48

- Autoimmune
- F > M (5:1)
- Etiopathogenesis: 2 phases
  - Inflammatory phase
  - Fibrotic phase



- Obliteration of vessel wall → vasculopathy



Tissue hypoxia

↓

Fibrosing growth factors are released

↓

Fibrosis

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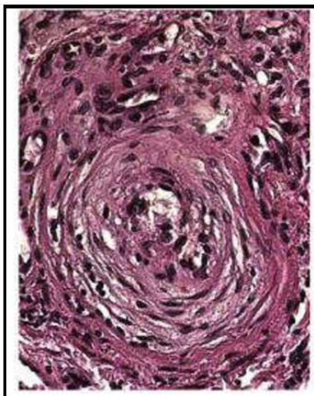

Fig: 3

Pulmonary arteriole

↓

Tunica media hypertrophy

Tunica intima thickening

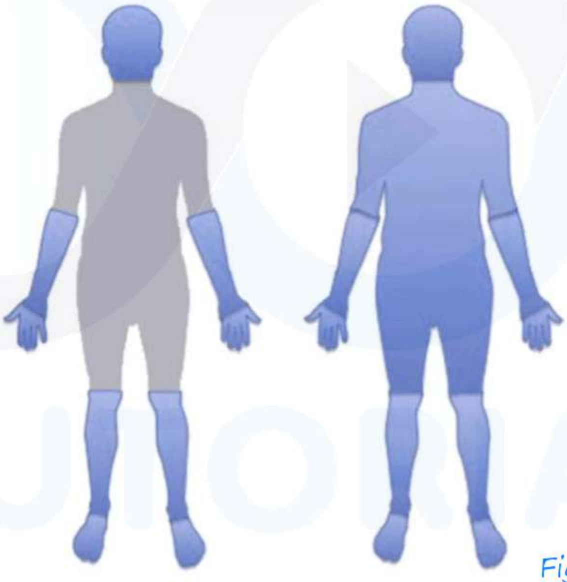

Fig: 4

Limited cutaneous Diffuse cutaneous form

Frequency of clinical organ involvement in limited cutaneous and diffuse cutaneous systemic sclerosis (SSc)

Features	Limited cutaneous SSc (%)	Diffuse cutaneous SSc (%)
Skin involvement	90°	100
Raynaud's phenomenon	99	98
Ischemic digital ulcers	50	25
Oesophageal involvement	90	80
Interstitial lung disease	35	65
Pulmonary arterial hypertension	15	15
Myopathy	11	23
Clinical cardiac involvement	9	12
Scleroderma renal crisis	2	15
Calcinosis cutis	–	–

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- Initial manifestation – Raynaud's phenomenon

↓

Episodic vasoconstriction

↓

Initial VC – pale

↓

Cyanosis (blue)

↓

Normal (red)

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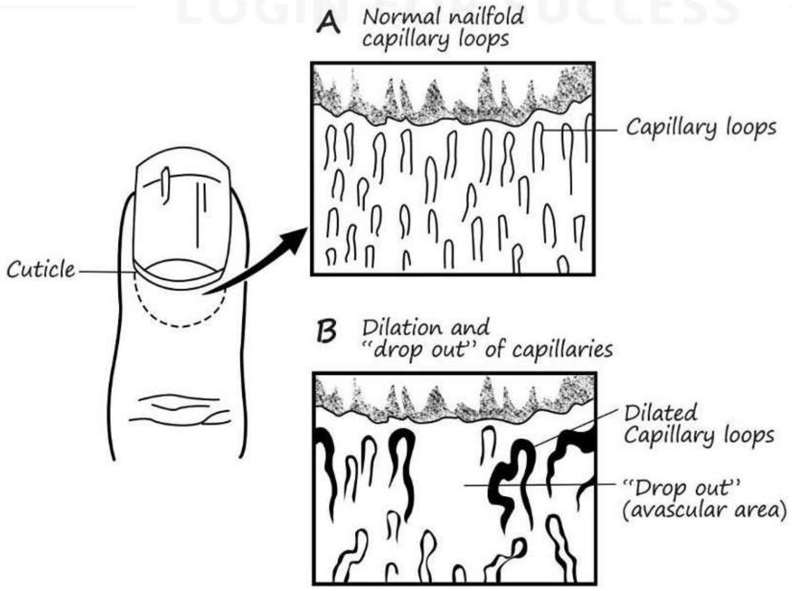
Raynaud's phenomenon

Primary	Secondary
Idiopathic	2° to connective tissue disease – SLE, systemic sclerosis
Reversible	Irreversible vessel damage
Positive family history	Vasculopathy

Fig: 5



Nailfold capillaroscopy Fig: 6

We can study capillary loops @ nail fold

↓

Nail fold capillaroscopy

Fig: 7

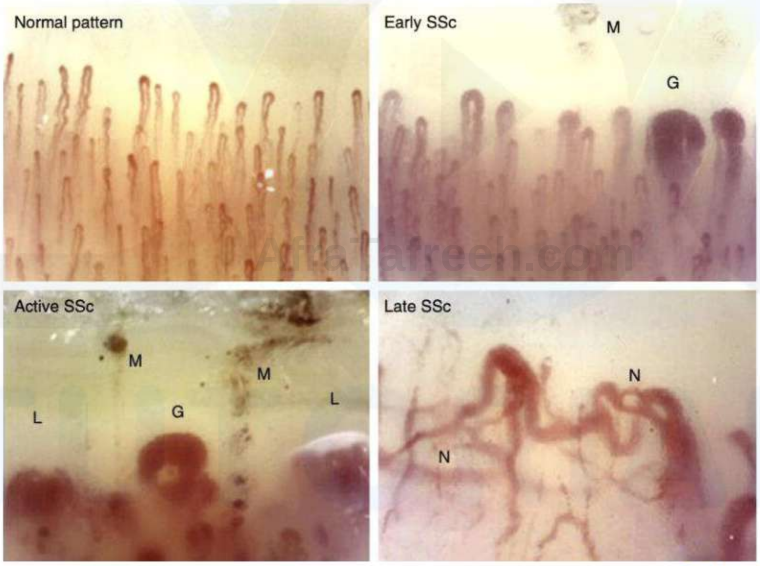


Fig: 8

Digital gangrene Fig: 9

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Stages of Raynaud's phenomenon Fig: 10

Acro-osteolysis – Terminal part dissolved Fig: 11

Sclerodactyly Fig: 12

Telangiectasia's over face Fig: 13

Periungual telangiectasias Fig: 14

Calcinosis cutis – most common in limited form Fig: 15

Calcinosis cutis – X-ray Fig: 16

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Crest Syndrome 00:25:03

- Limited cutaneous form associated with CREST syndrome
  - C – Calcinosis cutis
  - R – Raynaud's phenomenon
  - E – Oesophageal dysmotility
  - S – Sclerodactyly
  - T – Telangiectasia's

Fig: 17

Mask like facies

Masopf facies

↓

Mouse like

Fish mouth appearance

Fig: 18

Purse string appearance Fig: 19

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Fig: 20

Salt and pepper skin

↓

Depigmentation may spare perifollicular areas

GI Manifestations 00:30:41

- May involve oral → anal
- Oesophageal dysmotility
- Pseudo obstruction of intestine

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GAVE – Gastric Antra Valve Ectasia

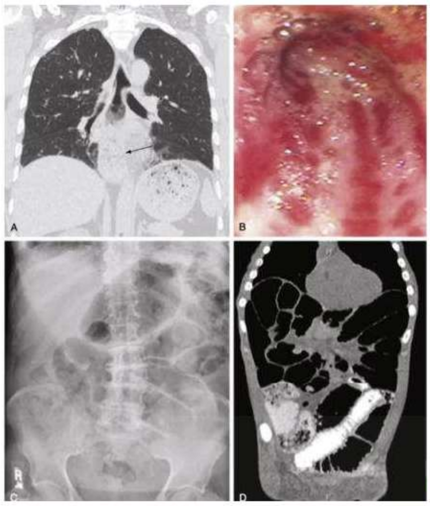

Fig: 21

- Esophageal dysmotility
- GAVE – watermelon stomach
- Dilated bowel loops
  - Intestinal pseudo-obstruction

Site	Principal manifestation
Oropharynx	Diminished oral aperture Dry mouth Periodontitis, gingivitis Swallowing
Esophagus	Reflux Dysphagia Strictures Barret's metaplasia
Stomach	Gastroparesis Gastric antral vascular ectasia (GAVE, watermelon stomach)
Small and large intestines	Bacterial overgrowth Diarrhoea/constipation Pseudo-obstruction Pneumatosis intestinalis Malabsorption Colonic pseudodiverticula
Anorectum	Sphincter incompetence

Lung Involvement 00:34:26

- Commonest → ILD → NSIP
- Pulmonary arterial HTN

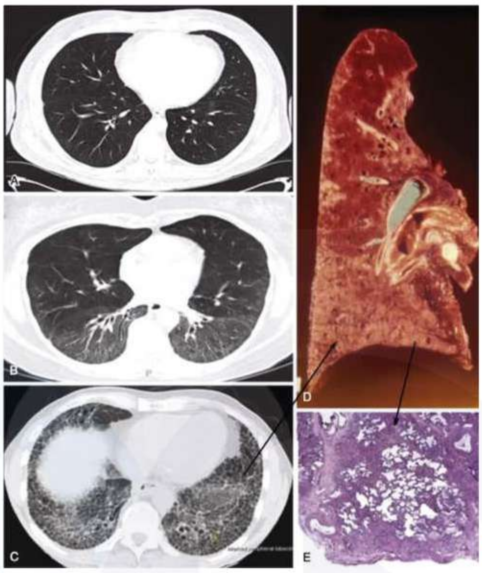

Fig: 22

- CT images
  - i. Normal
  - ii. ILD – Ground glass
  - iii. Extensive fibrosis
    - Restrictive pattern in pulmonary function tests
  - iv. Gross image
  - v. HPE image – Fibrosing alveolitis

Lung involvement Fig: 23

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- Most common causes of mortality → ILD

Renal Involvement 00:38:18

- Thrombotic microangiopathy

↓

MAHA (Schistocytes in peripheral smear)

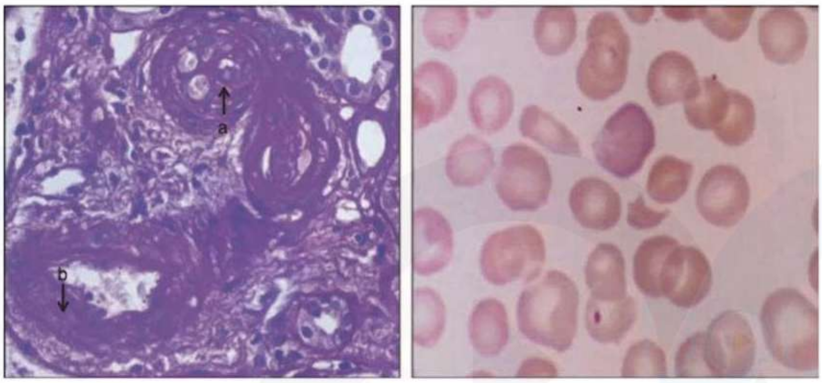

Fig: 24

- In early stages, we can use ACE inhibitors, prognosis improved
- Multi-system d/s

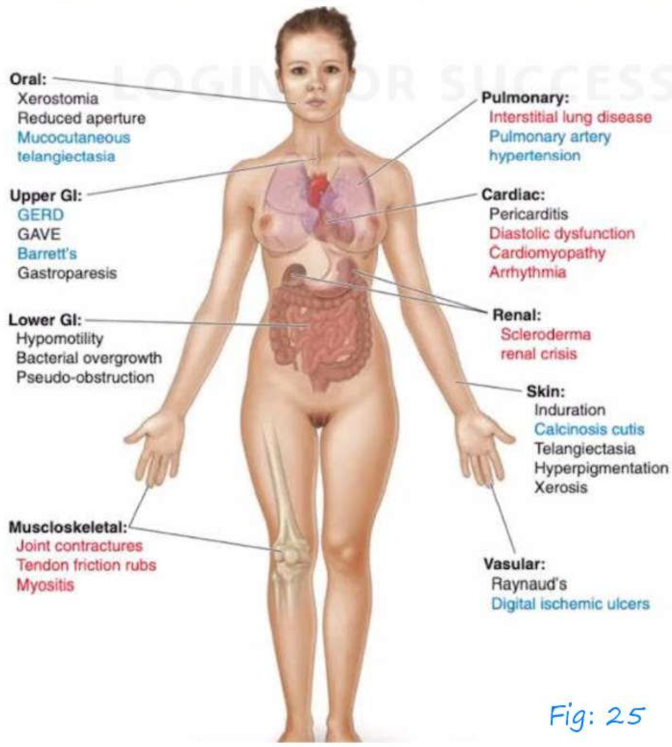

Fig: 25

- Palpable tendon friction rubs – Grating/leathery

Subsets of systemic sclerosis (SSC): Features of limited cutaneous SSc versus diffuse cutaneous disease 00:42:05

Characteristic features	Limited cutaneous SSc	Diffuse cutaneous SSc
Skin involvement	Indolent onset, limited to fingers, distal to elbows, face; slow progression	Rapid onset. Diffuse: Fingers, extremities, face =, trunk; rapid progression
Raynaud's phenomenon	Antedates skin involvement, sometimes by years; may be associated with critical ischemia in the digits	Onset coincident with skin involvement; critical ischemia less common
Musculoskeletal	Mild arthralgia	Severe arthralgia, carpal tunnel syndrome, tendon friction rubs; small and large joint contractures
Interstitial lung disease	Slowly progressive, generally mild	Frequent, early onset and progression, can be severe
Pulmonary arterial hypertension	Frequently, late, may occur as an isolated complication	Often occurs in association with interstitial lung disease
Scleroderma renal crisis	Very rare	Occurs in 15%; onset may be fulminant; generally early (<4years from disease onset)
Calcinosis cutis	Frequent, prominent	Less common, mild
Characteristic autoantibodies	Anti-centromere	Anti-topoisomerase I (Sci-70), anti-RNA polymerase III

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Major systemic sclerosis-specific autoantibodies and principal associated features 00:46:56

Target antigen	SSc Subset	Prominent characteristic clinical association
DNA Topoisomerase I (Sci-70) Speckled pattern	dcSSC	Tendon friction rubs, digital ischemia ulcers, scleroderma, extensive skin, involvement, early crisis
Centromere proteins Discreet speckled (centromere) pattern	icSSc	Digital ischemic ulcers, calcinosis cutis, isolated PAH; renal crisis rare
RNA polymerase III Speckled pattern	dcSSc	Rapidly progressive skin, tendon friction rubs, joint contractures, GAVE, renal crisis, contemporaneous cancers; digital ulcers rare
U3-RNP (fibrillarin) Nucleolar pattern	dc/IcSSc	PAH, ILD, scleroderma renal crisis, GI tract involvement, myositis
Th/T_o Nucleolar patten	IcSSc	ILD, PAH
PM/Sci Nucleolar pattern	IcSSc	Calcinosis cutis, ILD, myositis overlap
Ku Speckled pattern	Overlap	SLE, myositis overlap
U1-RNP Speckled pattern	MCTD	PAH, inflammatory arthritis, myositis overlap
U11/U12 RNP	dc/IcSSc	ILD

Treatment

- ACE inhibitors

Manifestation	Primary therapy	Alternative/second-line therapy
Raynaud's phenomenon	Vasodilators (CCB or PDE5 inhibitors) anti-platelet	PDE5 inhibitors, prostacyclin, ETA
Hypertensive renal disease	ACE inhibitors	ARBs, CCB, prostacyclin, rental transplant (wait atleast 12 months)
GI involvement	Upper GI Dental/periodontal care, lifestyle modifications, proton pump inhibitors, prokinetics	EGD to treat stenosis and/or GAVE
	Lower GI Probiotics, rotational antibiotics	Prokinetics Total parenteral nutrition
Skin	Mycophenolate mofetil, cyclophosphamide	IVIG, ATG, HSCT (severe, progressive cases), research trail
Interstitial lung disease	Mycophenolate mofetil, cyclophosphamide	Research trail (novel biologics and antifibrotic drugs)
Pulmonary arterial hypertension	PDE5 inhibitors, ETA, combination (PDE5i+ETA), prostacyclin, PRA, soluble guanylate-cyclase stimulators	Combination therapy, atrioseptostomy, lung transplant, research trial
Cardiac involvement	Heart failure therapy, diuretics, CCB	Immunosuppression, IVIG (myocardial inflammation)
Joints	Prednisone, methotrexate, TNF inhibitors, rituximab tocilizumab	MIG (if contractures and rubs are present), PT/OT
Muscles	Prednisone, methotrexate, azathioprine	IVIG

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SJOGREN'S SYNDROME

Introduction 00:00:13

- Autoimmune Disease
- Characterised by a chronic progressive course
- There is lymphocytic infiltration of exocrine glands

↓

Autoimmune exocrinopathy

Pathogenesis 00:01:50

- Activation of T cells (early part) and B cells (late part)
- All these cells will infiltrate into exocrine gland producing the manifestations of Sjogren's syndrome
- Also present with extra glandular manifestation's

Clinical features 00:02:56

- Middle aged female (F>M, 9:1)
- 2 Types
  - i. Primary
  - ii. Secondary
    - Associated with other diseases
    - Most common – Rheumatoid arthritis
    - SLE
    - Systemic Sclerosis
    - MCTD
    - 1° biliary cirrhosis
    - Autoimmune thyroid D/S
    - Chronic active hepatitis

Clinical Feature

- Extra-glandular
- Glandular manifestations

↓

Involvement of Salivary gland

i. Dry mouth – Xerostomia
ii. Burning sensation of oral mucosa
iii. Dry & erythematous oral mucosa
iv. Difficulty in Swallowing

Fig: 1

- B/L parotid gland enlargement

  ↓

  1° Sjogren's syndrome (2/3 patients have parotid enlargement)

Involvement of lacrimal gland

i. Dry eyes – (Keratoconjunctivitis sicca)

   ↓

   - Foreign body sensation
   - Itching
   - Redness
   - Photophobia

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Extra glandular manifestations

- Lung involvement
  - Small air ways
  - ILD-NSIP
  - Lymphocytic interstitial pneumonitis
- Kidney
  - Tubulo – Interstitial involvement
  - Glomerular involvement can occur when associated with immune complex mediated d/s like cryoglobulinemia
  - Renal tubular acidosis type I (Distal RTA)

Indictors of Sjogren's

1. Persistent parotid enlargement
2. Purpura
3. Cryoglobulinemia
4. Leucopenia
5. Low C4 levels
6. Anti-Ro (SS-A)
7. Anti La (SS-B)

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- If an individual has anti-Ro & Anti-La positive

↓

More severe disease

Diagnosis 00:17:48

- Antibodies – Anti Ra & Anti La

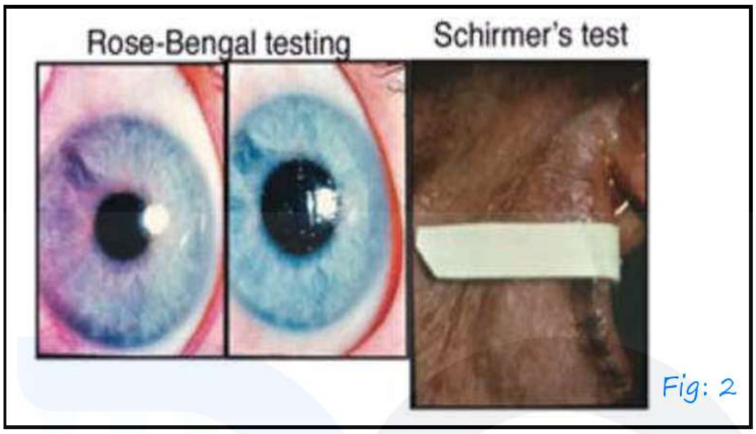

Fig: 2

- Schemer's test → To pick up whether patient has dry eyes
- Rose Bengal testing – For detecting corneal erosion

2016 American collage of rheumatology/European league against rheumatism classification criteria for Sjogren's syndrome

Item	Score
Histopathology showing focal lymphocytic sialadenitis with a focus score ≥1 per 4 mm²	3
The presence of anti-Ro/SS-A antibodies	3
SICCA ocular staining score ≥5 using lissamine green and fluorescein dye (or Rose Bengal score ≥4 by the van Bijsterveld scoring system)	1
Schirmer's test <5 mm per 5 minutes in at least one eye	1
Unstimulated whole salivary flow of less than 0.1 mL per minute	1

Rules for Classification

- Patients may be classified as primary Sjögren's syndrome if they display at least one symptom of ocular or oral dryness and a total score of 4 or greater when the weights from the five criteria items above are summed.

Exclusion Criteria

- History of head and neck radiation treatment
- Active hepatitis C infection (with confirmation by PCR)
- AIDS
- Sarcoidosis
- Amyloidosis
- Can go for minor salivary gland biopsy

↓

Lymphocytic infiltration (+)

Differential diagnosis 00:22:09

HIV infected and SICCA syndrome	Sjogren's syndrome	Sarcoidosis
Predominant in young males	Predominant in middle aged to women	No age or sex preference
Lack of autoantibodies to Ro/SS-A and/or La/SS-B	Presence of anti-antibodies	Lack of autoantibodies to Ro/SS-A and or La/SS-B
Lymphoid infiltrates of salivary glands by CD8+ T lymphocytes	Lymphoid infiltrates of salivary glands by CD4+ T lymphocytes	Granulomas in salivary glands
Association with HLA-DR5	Association with HLA-DR3 and DRW52	Unknown
Positive serologic tests for HIV	Negative serologic tests for HIV	Negative serologic tests for HIV

Treatment 00:23:26

- Supportive therapy
- Dry eyes – Artificial tears – Methyl cellulose drops
- Dry mouth – water, saliva substitutes
- Joint involvement – HCQ/Methotrexate + Steroids
- ILD – Cyclophosphamide pulse therapy.

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SARCOIDOSIS

Introduction 00:00:19

- Multisystem inflammatory disorder
- Characterised by non-caseating granulomas
- Diagnosis with non-caseating granulomas
  - Berylliosis
  - Cat scratch disease
- Most common in females

Etiopathogenesis 00:02:08

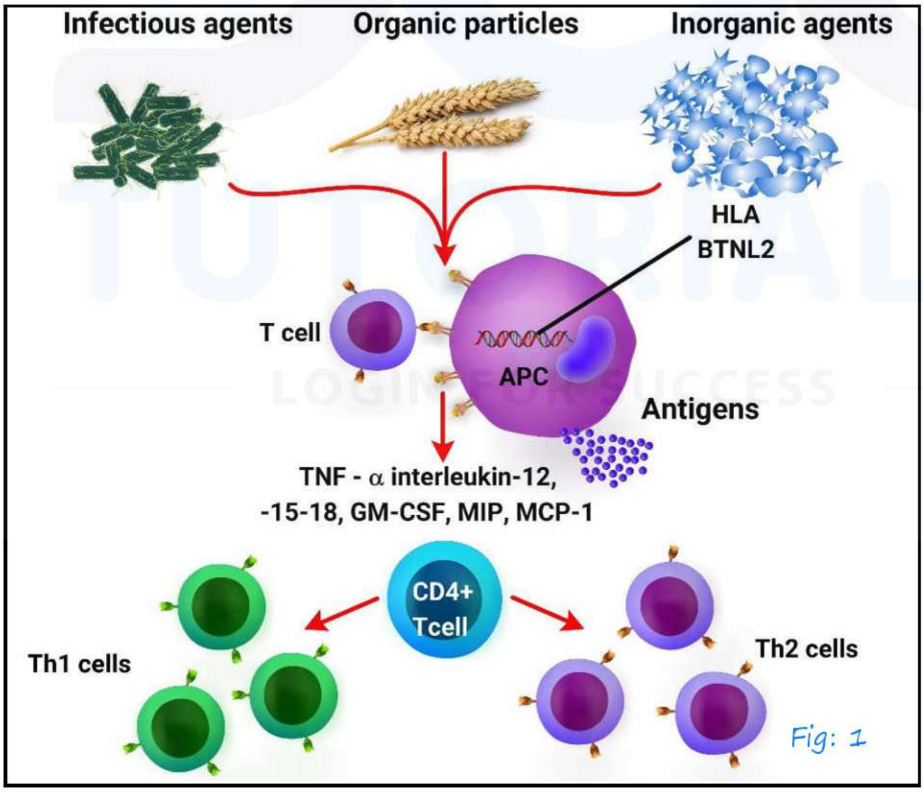

Fig: 1

- Source of antigen may be infectious antigen
  - Organic particle
  - Inorganic agents

- One of the infection agent – Propionibacterium acnes
- Mycobacterial protein mkatG detected on surface of granuloma

Exposure to antigen

↓

APC present this antigen to T cells

↓

CD_4 cells activated

↓

Overproduction of Th_1 cells & Th_2 cells

↓

Release of cytokines (IL-2, INF5, IL-4,5,6,10)

↓

Granulomas

- **D/S can progress**
- **Resolve spontaneously as well**

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Clinical features 00:06:10

Clinical features

Chronic

↓

Common form

Acute

↓

1. Lofgren's syndrome

- Erythema nodosum
- Bilateral lymphadenopathy
- Arthritis

2. Heerford's syndrome

- Bilateral LMN facial palsy
- Parotitis
- Uveitis

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Chronic

- Most common organ – Lungs
- 2nd most common – skin
- Next – eyes

Lung involvement

- Almost 90% cases
- Cough
- Dyspnea
- Staging system – based on CXR → scadding's staging system

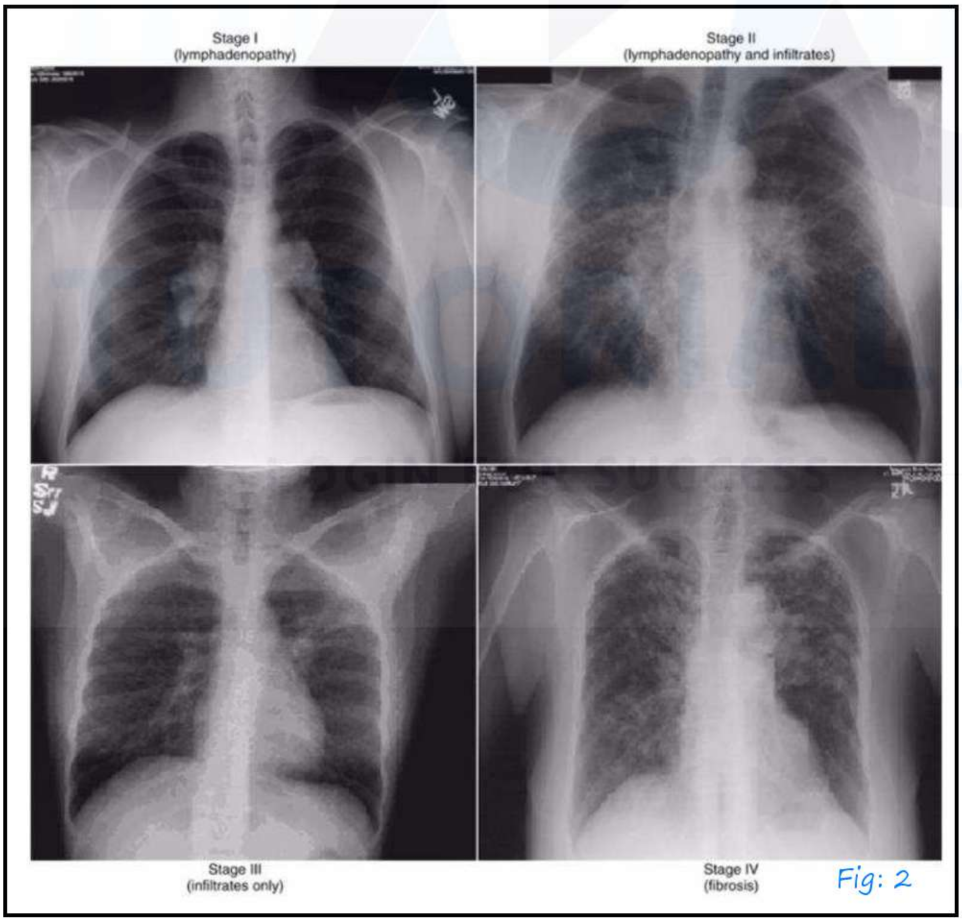

Fig: 2

- Stage I: Bilateral hilar lymphadenopathy
- Stage II: Bilateral hilar lymphadenopathy + Pulmonary infiltrates
- Stage III: Pulmonary infiltrates only
- Stage IV: Pulmonary fibrosis

- In sarcoidosis → upper lobe predominant fibrosis
- ICD in sarcoidosis → NSIP pattern

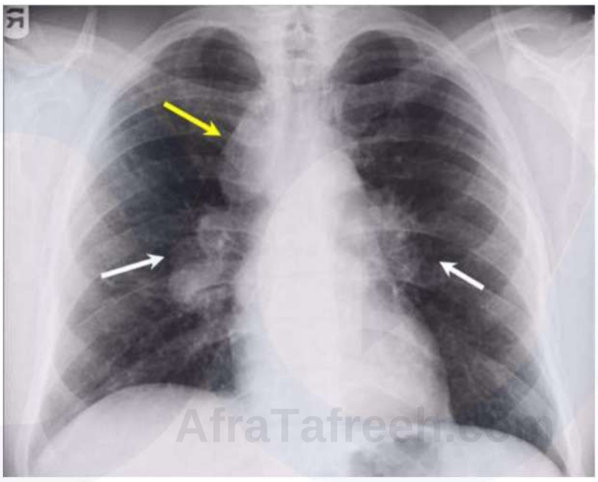

Fig: 3

Garland's sign
↓
Bilateral hilar lymphadenopathy +
right paratracheal node involvement

Skin involvement

i. Lupus pernio:

- Chronic inflammatory skin lesions which are predominantly in the form of reddish papules over face

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Fig: 4

ii. Erythema nodosum: Tender raised erythematous lesions

Fig: 5

Eye involvement

- Most common – anterior uveitis
- Others – posterior uveitis and retinitis

Neurological manifestations (neuro sarcoidosis)

- Bilateral LMN facial palsy → D/D
  i. Sarcoidosis
  ii. GBS
  iii. Lyme d/s
  iv. Diphtheria
- Optic neuritis

- Hypothalamic involvement
- Pituitary stalk involvement
- Basal meningitis
- Transverse myelitis

Heart

- Rare
- Cardiomyopathy – Restrictive > Dilated
- Arrhythmias

Kidneys

- Tubulointerstitial involvement

Metabolic

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- Hypercalcemia
- Granulomas → 1,25 dihydroxy cholecalciferol
  - Because of production of 1,25 dihydroxycholecalciferol by granulomas per se

↓

Hypercalcemia

↓

Renal involvement

Bone marrow

- Lymphopenia
- Anaemia of chronic disease

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Liver

- Granulomatous hepatitis
- Cholestasis
- Most common – increase ALP

Frequency of common organ involvement and lifetime risk

	Presentation, %	Follow-up, %
Lung	95	94
Skin	24	43
Eye	12	29
Extrathoracic lymph node	15	16
Liver	12	14
Spleen	7	8
Neurologic	5	16
Cardiac	2	3

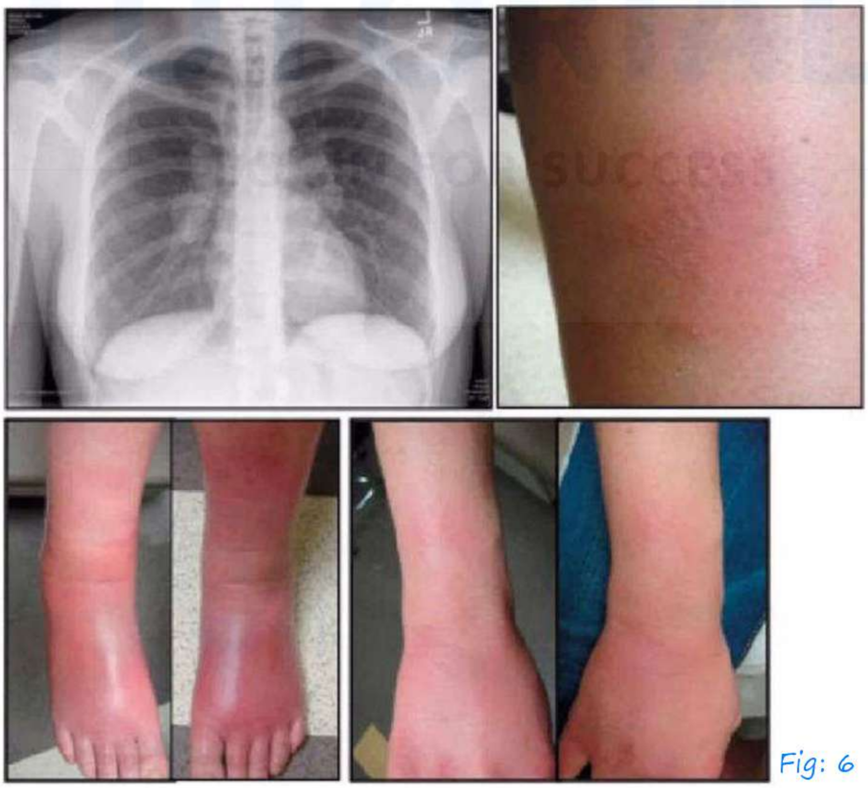

Fig: 6

- Bilateral hilar lymphadenopathy
  - Rash
  - Arthritis
  - Lofgren's syndrome

Investigations 00:28:31

- CXR
- CT thorax
- Serum ACE levels → increased (not specific)
  - Hyperthyroidism, gaucher's d/s, leprosy, military TB
- PET scan
- Biopsy → Granulomas
  - Endobronchial biopsy/transbronchial biopsy

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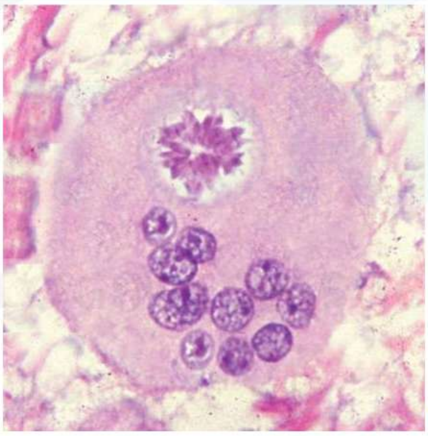

Fig: 7

Stellate inclusions
↓
Intracytoplasmic

— Asteroid bodies

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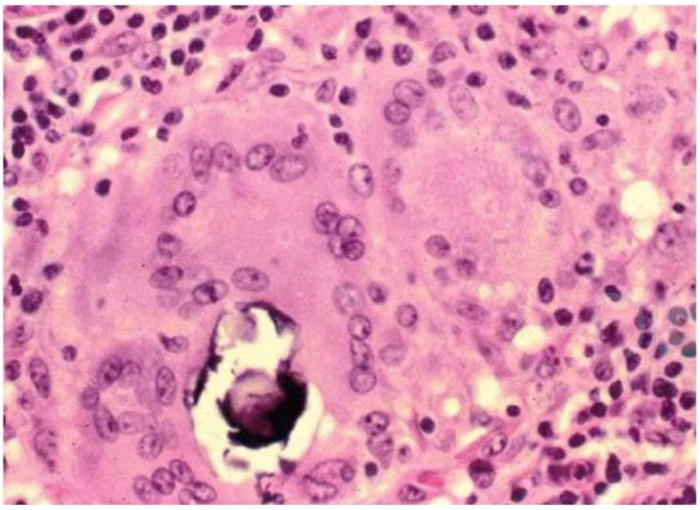

Fig: 8

Deposition of calcium + protein

↓

Schaumann bodies

- BAL study → Bronchoalveolar lavage
  - Increase lymphocytosis
  - Increase CD_4: CD_8 ratio
- Gallium scan

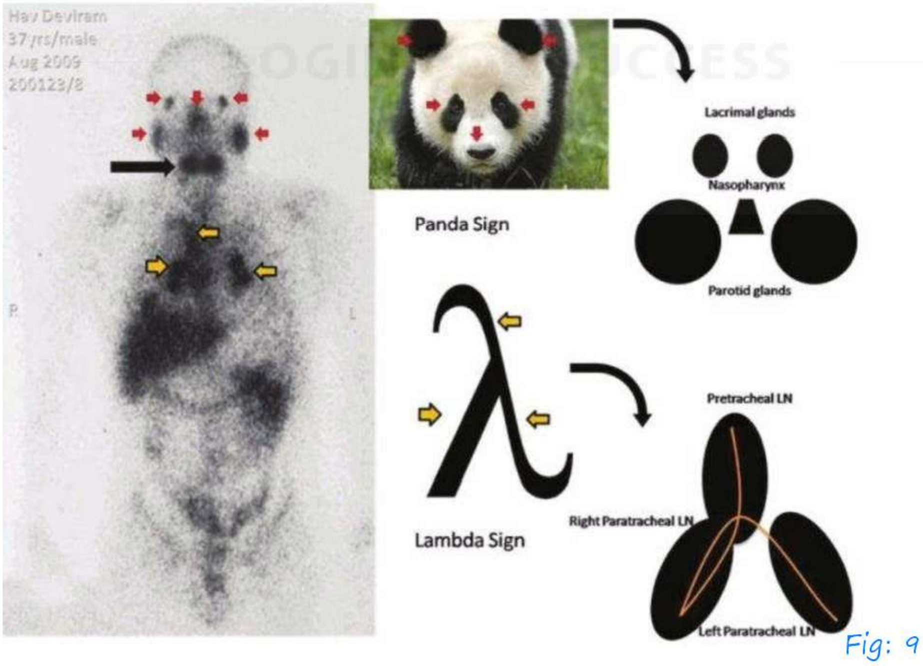

Fig: 9

- Panda sign – Involvement of lacrimal and parotid gland
- Lambda sign – Involvement of right and left paratracheal LN and pretracheal LN

Treatment 00:38:31

Algorithm for management of sarcoidosis

Acute disease

Minimal to no symptoms	Single organ disease	Symptomatic multiple organs
↓	↓	↓
Abnormalities of neurologic, cardiac, ocular, calcium	Affecting only: anterior eye, localized skin, cough	Systemic therapy: glucocorticoids (Example., prednisone)
↓	↓	↓
Yes: consider systemic therapy No: no therapy and observe	Yes: try topical steroids No: systemic therapy	Taper to <10 mg is less than 6 months: continue prednisone Cannot tapper to <10 mg in 6 months or glucocorticoid toxicity
		↓
		Consider methotrexate, hydroxy chloroquine, azathioprine

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Management

Management of algorithm of chronic disease

Glucocorticoids tolerated
↓
Dose <10 mg/d
↓
Yes: continue therapy
No: seek alternative agents

Glucocorticoids not tolerated
↓
Alternative agents
↓
Methotrexate
Hydroxychloroquine
Azathioprine
Leflunomide
Mycophenolate
Minocycline

Glucocorticoids not effective
↓
Try alternative agents
↓
If effective, taper off glucocorticoids
If not effective consider:
Multiple agents
Infliximab
Cyclophosphamide
Thalidomide

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IgG4 RELATED DISEASE

- Immune mediated
- Multisystem disorder
- Inciting agent? unknown
- As a result of exposure to some tigering factors
- These occur T cell, B cell interactions
- Production of various cytokines
- Cytokines → fibrotic process (Tumor like Lesion)
- Plasma cell activation → Dominant IgG4 response

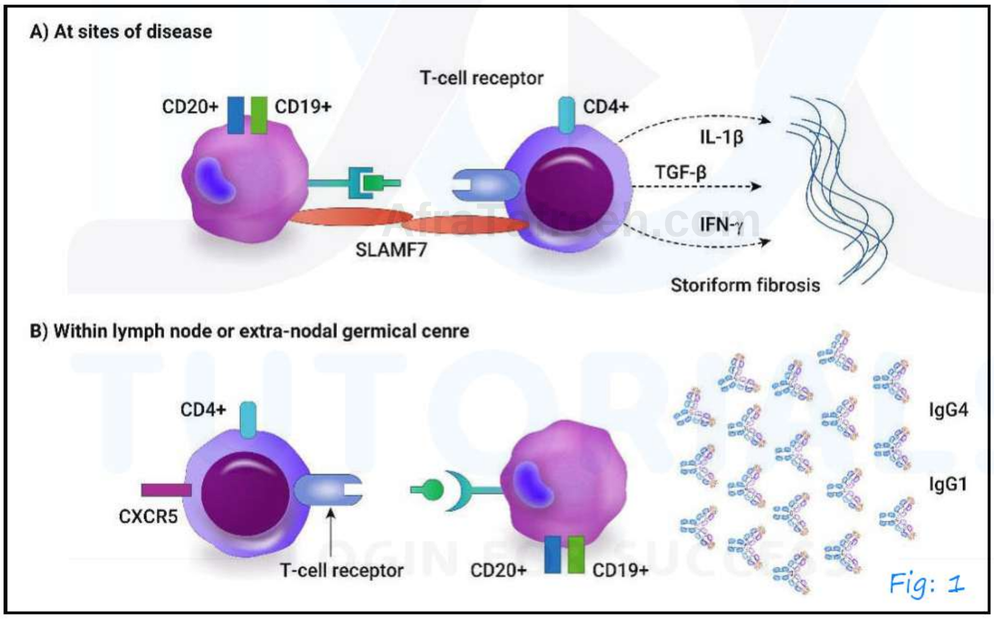

Fig: 1

Clinical factor 00:05:11

- Lacrimal glands
- Salivary glands
- Thyroid → Riedel's thyroiditis →firm to hard thyroid
- CNS – meninges, Pituitary stalk
- Lungs → ILD, tumor like lesion
- Liver

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- Biliary system
- pancreas → sausage shaped pancreas
- Retroperitoneal – ormond disease
- Prostate

Fig: 2

Fig: 3

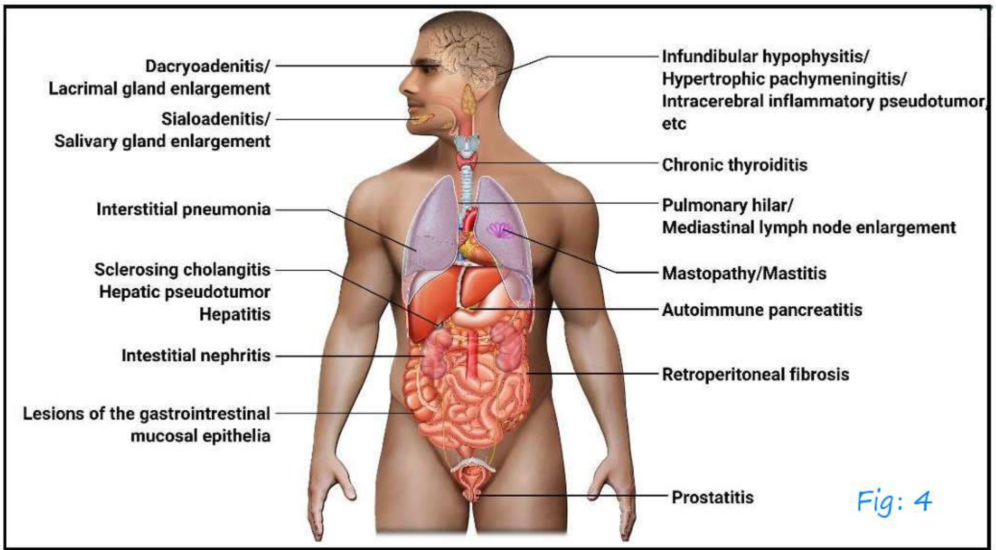

Fig: 4

- Auto immune pancreatitis
- Ormonds disease
- Mikulicz syndrome
- Tolasa-Hunt syndrome

Investigation 00:12:29

- Serum IgGu – increase
- Retroperitoneal fibrosis

Biopsy → gold standards

i. Lymphoplasmacytic infiltrate

ii. Storiform fibrosis

iii. Obliterative phlebitis

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IHC- IgG4

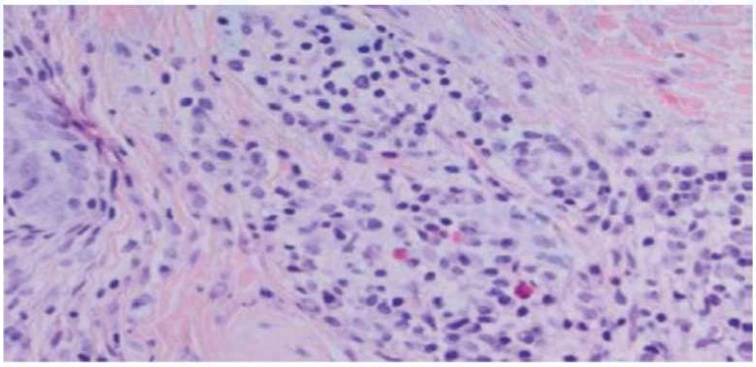

Fig: 5

Treatment

- D.O.C → steroid
- 2003 → Japan
- Rituximab → anti-CD 20 for pts not responding to steroids

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RHEUMATOID ARTHRITIS

Introduction 00:00:28

- Most common chronic inflammatory
- Symmetrical polyarthritis
- Skeletal and extra skeletal manifestations

Etiopathogenesis 00:01:43

- Multifactorial
  - Genetic
  - environmental
- F > M
- 25-55 years
- Genetic
  - HLA DR4 (main)
  - HLA DR1
- Environmental – smoking
- Porphyromonas gingivalis
- Prevotella

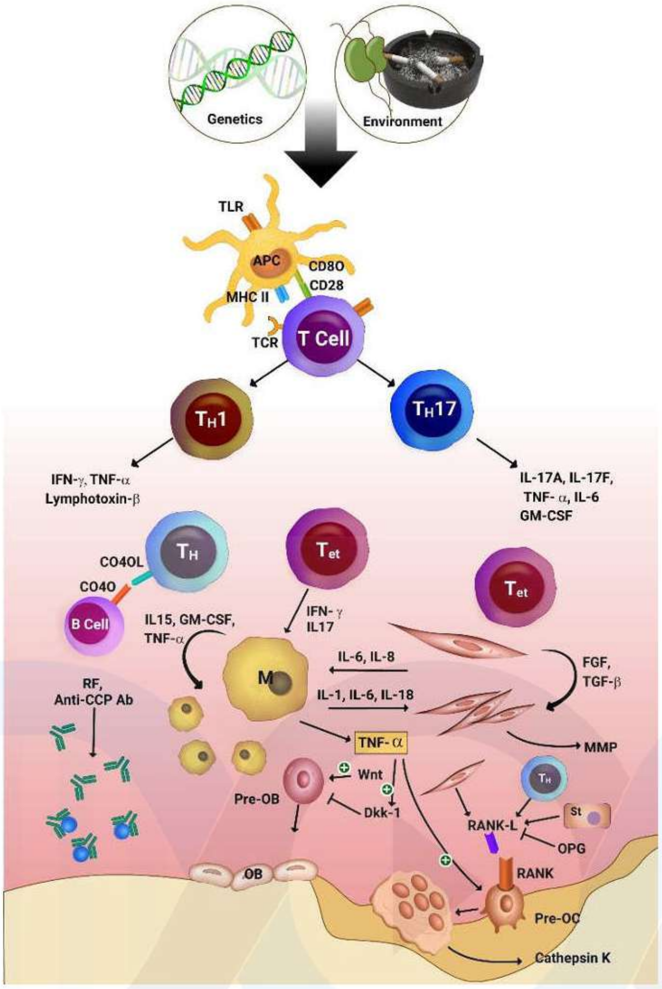

Fig: 1

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Antigen presenting cells

↓

Activation of TH1 > TH17

↓

Release of cytokines

↓

Activates B cells

↓

Antibodies

- Rheumatoid factor
- Anti CCP (cyclic citrullinated peptide)

- Rheumatoid factor → Ig M against Fc of Ig G

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- Macrophage also activated

  ↓

  TNF-α → activation of osteoclasts

  ↓ ↓

  Pivotal cytokine   bone erosion

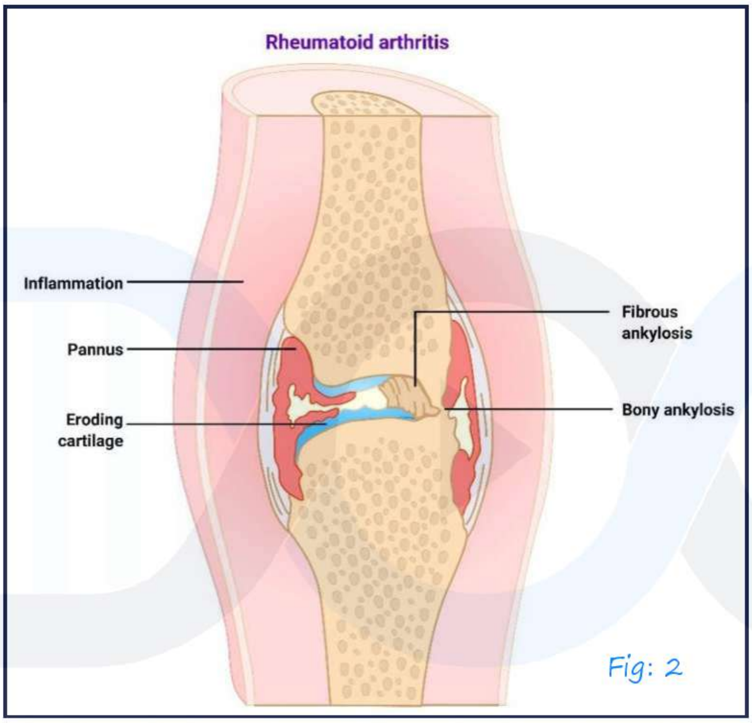

Fig: 2

- 1° site of pathology – synovium

  Bone – synovitis

  ↓

  Pannus (Inflammatory mass)

  ↓

  Responsible for destruction of bones, cartilages, ligaments

Clinical features 00:10:40

Pre-RA → Early non-specific symptoms

Pre-RA → Skeletal manifestations, Extra skeletal manifestations

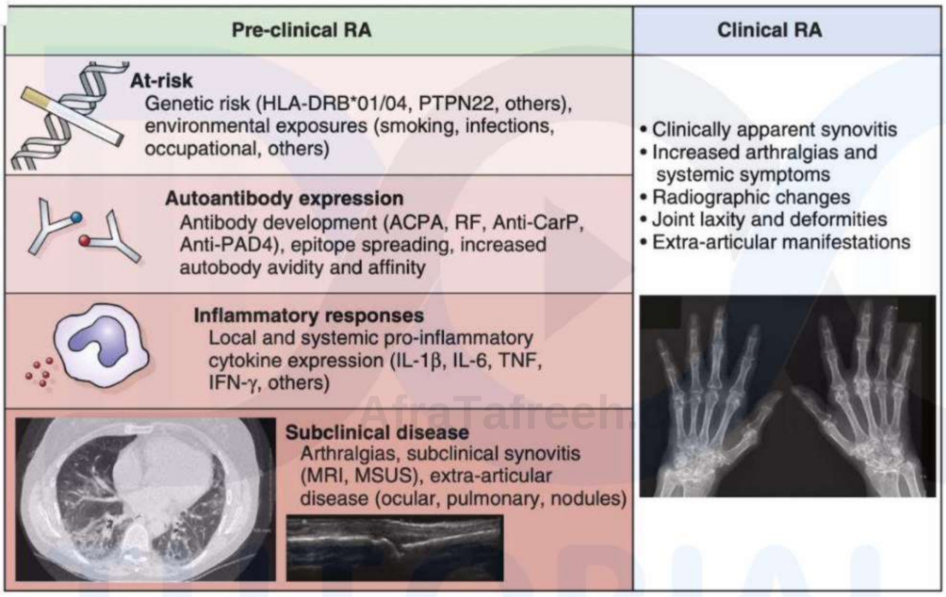

Fig: 3

- Final stages of RA – Burnt out RA

Skeletal manifestations

- B/L symmetric polyarthritis
- Predominantly involves small joints hands and feet
- Early joints involved
  - MCP
  - Wrist joint

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The most common joints involved during the course of rheumatoid arthritis			
MCP PIP Wrist Knee Shoulder MTP	90%-95% 75%- 90% 75%- 80% 60%- 80% 50%- 70% 50%- 60%	Ankle/subtalar Cervical spine (esp.c1-c2) Elbow Hip Temporoma ndibular	50%-60% 40%-50% 40%-50% 20%-40% 10%-30%

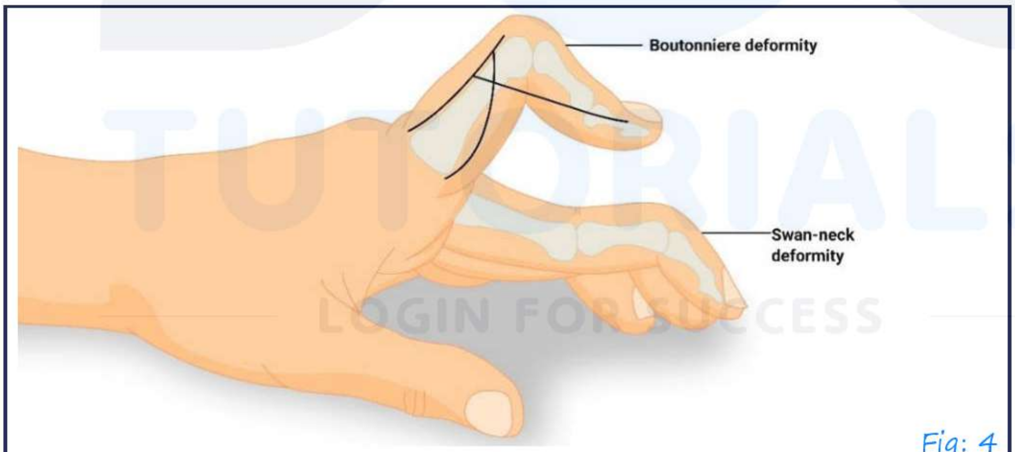

Fig: 4

- Boutonniere deformity
  - Flexion at PIP
  - Extension at DIP
- Swan neck deformity
  - Flexion at DIP
  - Extension at PIP

- Z deformity/hitchhiker thumb
  - Hyperextension of IP of thumb subluxation of first MCP joint

Fig: 5

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- Zig-zag deformity
  - Radial deviation of metacarpals
  - Ulnar deviation of fingers

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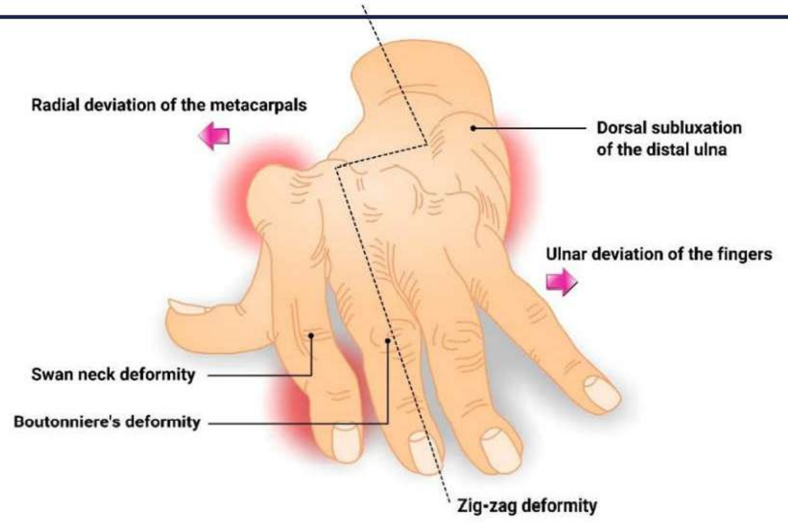

Fig: 6

- Swan neck deformity

Fig: 7

- Boutonniere deformity
  - Z deformity of thumb

Fig: 8

- Pianokey deformity
  - Due to rupture of extensor carpi ulnar is tendon

Fig: 9

- Metatarsophalangeal joint (most common in LL)

Fig: 10

- Arthritis associated with psoriasis – erosive arthritis

Fig: 11

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Extra skeletal manifestations

- Atlantoaxial subluxation (C1 – C2)
  - Cervical myopathy
- Carpal tunnel syndrome

Fig: 12

Ocular manifestations

- Keratoconjunctivitis sicca → most common
- Episcleritis
- Scleritis
- Scleromalacia perforans

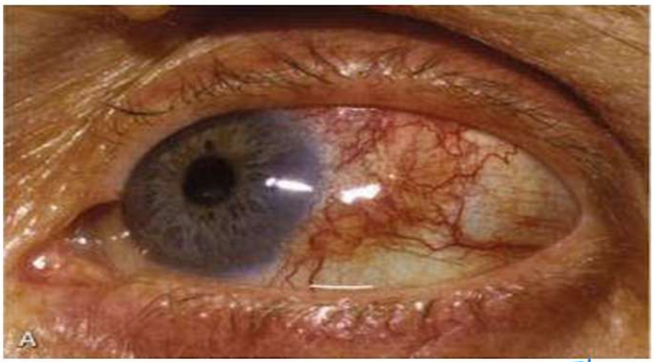

Fig: 13

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Skin manifestations

- Rheumatoid nodules (most common)
- Purpura
- Pyoderma gangrenosum

Rheumatoid nodules

- Seen in 30-40% of RA
- Painless nodules
- Predominantly on extensor aspect over elbow achilles tendon
- Most common in individuals with RA factor positivity
- Subcutaneous nodules → can undergo ulceration, necrosis
- Nodules may be present in lung also

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Fig: 14

Lung involvement

- Pleuritis (most common)
- Pleuritis with or without effusion

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- Exudative effusion with lymphocyte predominant, low sugar values
- ILD – UIP – usual interstitial pneumonia (most common)
- ILD – NSIP – Nonspecific interstitial pneumonia

CT - Thorax

- UIP – Honey comb appearances
- NSIP – Ground glass opacities

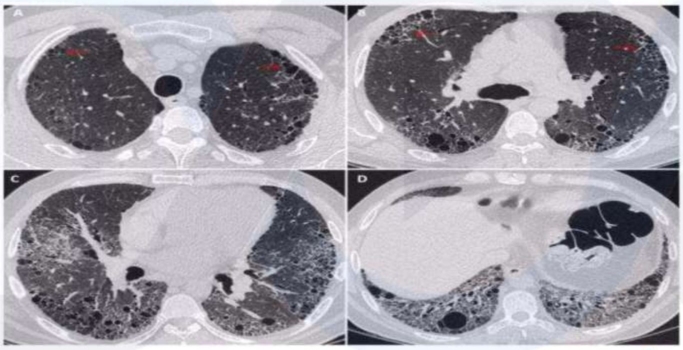

Fig: 15

- Rheumatoid arthritis + pneumoconiosis → caplan's syndrome
- Bronchiolitis
- Bronchiectasis

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Hematological manifestations

- Most common – normocytic normochromic anemia
- Felty's syndrome
  - Nodular RA
  - Neutropenia
  - splenomegaly
- Large granular lymphocytic leukemia

- DLBCL – Diffuse large B cell lymphoma (most common)

Cardia manifestations

- Pericardium – most common involved – pericarditis
- Increased risk of atherosclerosis
- Increased risk of CAD – most common cause of death
- Most common valvular lesion – mitral regurgitation

Renal manifestations

- Most common
  - Membranous nephropathy
  - Secondary amyloidosis

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GI manifestations

- 2° to vasculitis – mesenteric ischemia

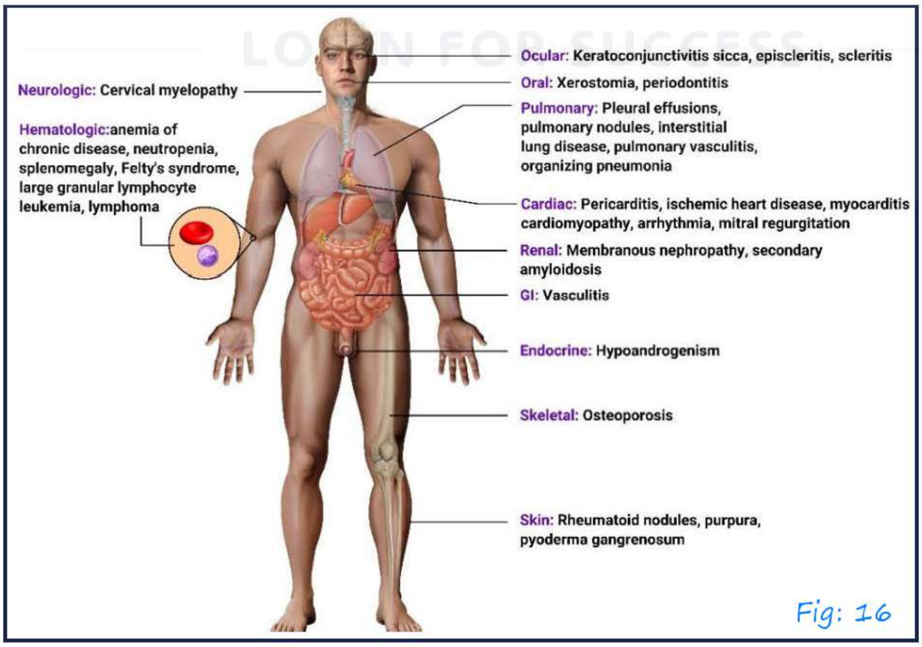

Fig: 16

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Diagnosis 00:43:29

- Early morning stiffeners – would last for one hour
- RA factor
- Anti CP – most specific
- CRP – C- reactive protein
  - Indicative of active joint inflammation
- X – ray

Classification criteria (2010 – ACR-EULAR)

- Score ≥ 6 points – definite RA

Classification criteria for rheumatoid arthritis		
		Score
Joint involvement	1 Large joint (Shoulder, elbow, hip, knee, ankle) 2-10 large joints 1-3 small joints (MCP, PIP, thumb IP, MTP, wrists) 4-10 small joints >10joints (at least 1 small joint)	0 1 2 3 5
Serology	Negative RF and negative ACPA Low-positive RF or low positive anti-CCP antibodies (≤	0 2

Treatment 00:50:23

- DMARDS → Disease modifying anti rheumatoid drugs

Conventional synthetic DMARDs
Hydroxychloroquine Leflunomide Methotrexate Sulfasalazine
Target synthetic DMARDs
Baricitinib Tofacitinib
Biological DMARDs
TNF alpha inhibitors
Adalimumab Certolizumab pegol Etanercept Golimumab Infiximab
Anti-B-Cell (CD20)
Rituximab
Anti T cell costimulation (CD80, CD86)
Abatacept
Anti-Il-6
Sarilumab Tocilizumab

- Methotrexate → DOC: - 10-25mg weekly

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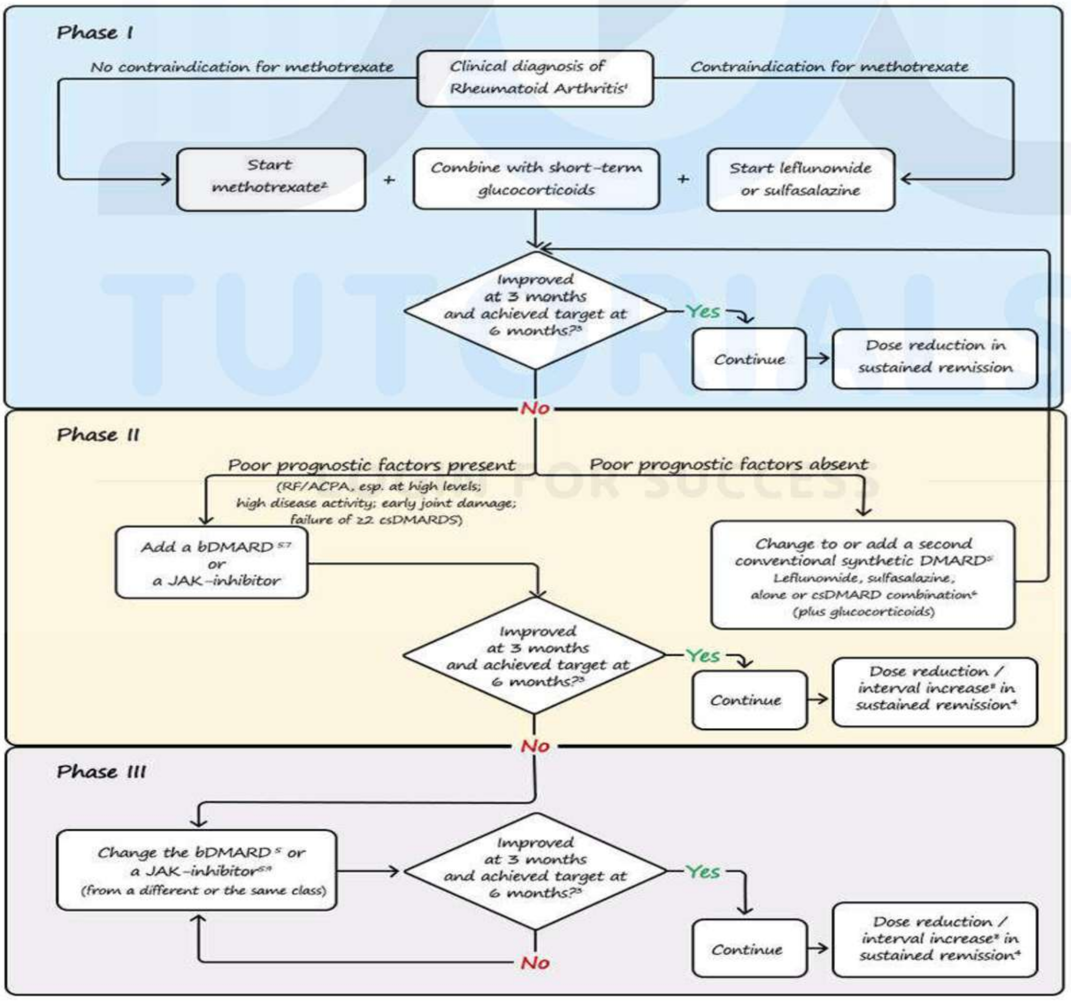
- To reduce toxicity – folic acid

- Sulfa-saline → 500mg 1-0-1 → lg 1-0-1
- HCQ's → 200-400mg/day → Doc in pregnancy

  Side effects – Retinal toxicity → Bull's eye maculopathy.

Recommendation

- EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease – modifying antirheumatic drugs: 2019 update:



SERONEGATIVE SPONDYKOARTHRITIDES

Introduction 00:01:26

- Group of disorders having common
  - Clinical features
  - Genetic factors
  - Pathogenic mechanisms
    - i. Ankylosing spondylitis
    - ii. Reactive arthritis
    - iii. Psoriatic arthritis
    - iv. Enteropathic arthritis
    - v. Juvenile spondyloarthritis
    - vi. Undifferentiated spondyloarthritis

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Common features 00:03:00

- Axial predominant – involves spine, pelvis, ribcage
- Asymmetric oligoarthritis
- HLA B-27 positivity
- Strong tendency for familial aggregation
- Enthesitis-Inflammation of enthesis

  ↓

  Tendons, ligaments, joint capsule
- Sacroiliitis
- Anterior uveitis
- RA factor, anti CCP negative
- No extra articular features of RA

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Classification 00:06:37

Sacroiliitis on imaging plus ≥1 SpA feature	Or	HLA-B27 plus ≥2 other SpA features
Sacroiliitis on imaging • Active (acute) inflammation on MRI highly suggestive of SpA – associated sacroiliitis[b] And/or • Define radiographic sacroiliitis according to modified New York criteria		SpA features • Inflammatory back pain[d] • Arthritis • Enthesitis (heel)[f] • Anterior uveitis • Dactylitis[e] • Psoriasis • Crohn's disease or ulcerative colitis[e] • Good response to NASIDs[h] • Family history of SpA • HLA-B27 • Elevated CRP

Ankylosing spondylitis 00:09:44

- Prototype disorder
- M > F
- Age: 2nd–3rd decade

Etiopathogenesis

- Genetic: HLA B27 (75-90%)

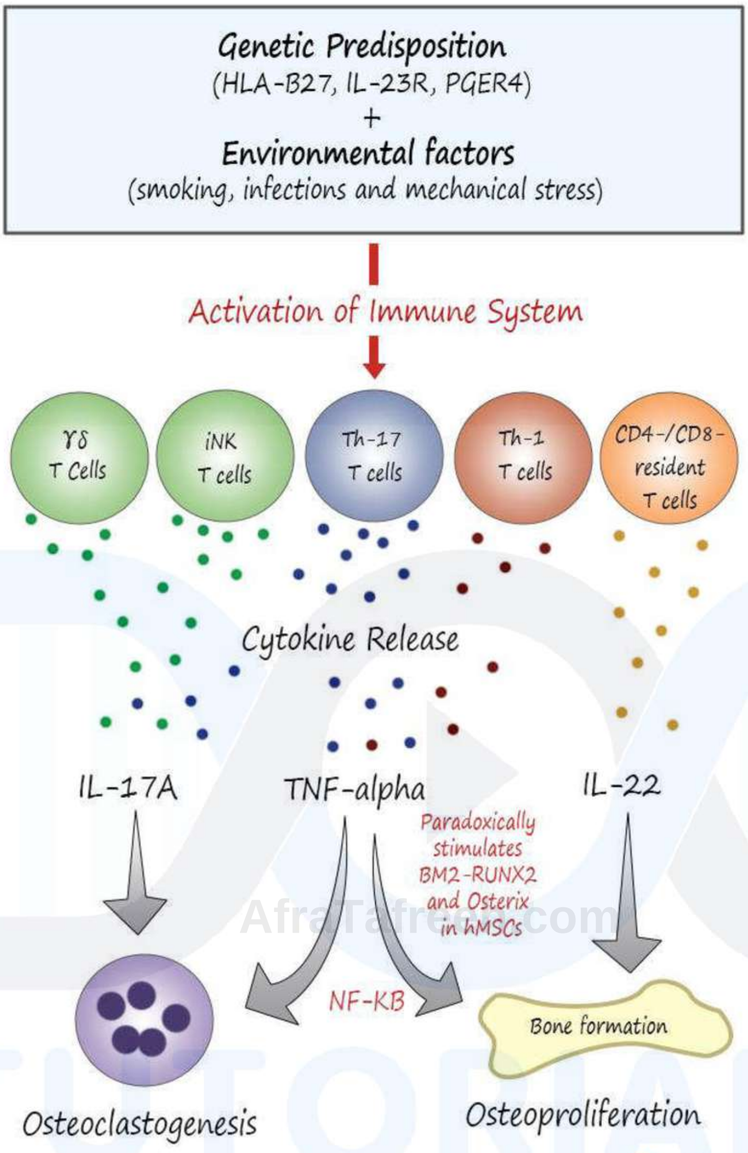

Fig: 1

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- Most important cytokine → TNF-α

Clinical features

- Low backache (lower lumbar & gluteal region)
- Inflammatory backache
- Sacroiliitis

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	Inflammatory LBP	Mechanical LBP
Age of onset, year	<40	Any age
Type of onset	Insidious	Acute (typically after injury)
Symptom duration	>3 months	<4 weeks
Morning stiffness	>60 minutes	<30 minutes
Nocturnal pain	Frequent	Absent
Effect of exercise	Improvement	Exacerbation
Effect of rest	Exacerbation	Improvement
Back mobility	Loss in all planes	Abnormal flexion
Alternating buttock pain	Present in early disease	Not present

- 30% cases – peripheral arthritis
- Affection of costo vertebral joints → chest wall limitation

O/E

- Tenderness over sacroiliac joint
- Decreased chest expansion (N – >5cm)

Modified schoeber's test

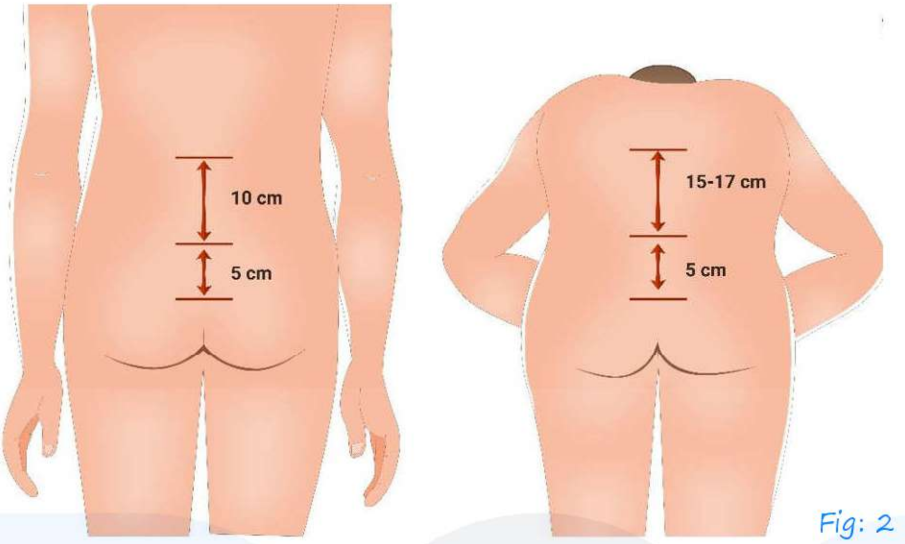

Fig: 2

Identify the posterior superior iliac spine and join both the lines

↓

Draw a line 5cm below and 10cm above this line

↓

Ask the patient to flex forward – sometimes it will be difficult to flex

↓

Normal person – distance increase → 22cm

↓

In AS – 17cm – limitation of spinal flexion

- Formation of syndesmophytes because of ossification of annular fibrosis, 2 spinous ligaments

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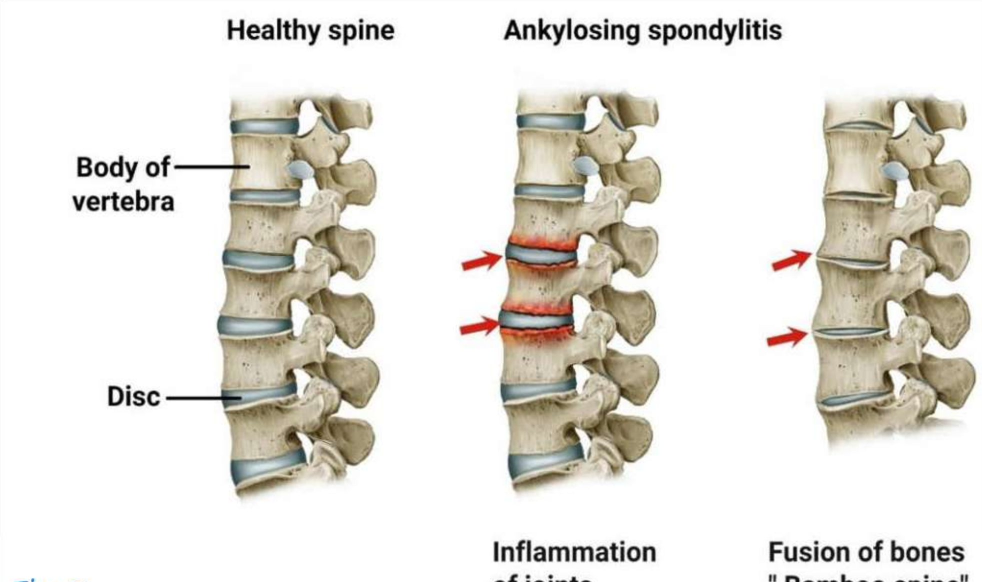


Fig: 3

Extra skeletal manifestations

- Most common – acute anterior uveitis (30-40%)
- Apical fibrosis
- Aortic regurgitation
- Amyloidosis
- Colitis
  - For assessing the severity – BASDAI scoring system

↓

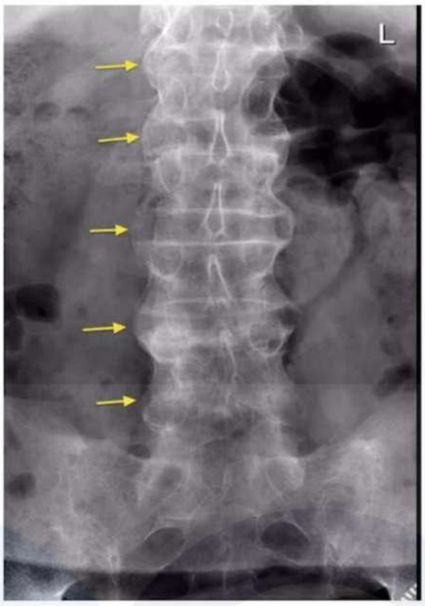
Bath ankylosing spondylitis disease activity index

- ASDAI scoring system

Treatment

- First choice → NSAID's
- TNF-α inhibitors
  - i. Infliximab
  - ii. Etanercept
- IL-17A – Secukinumab

- Sulfasalazine



Bamboo spine Fig: 4

Fig: 5

Classification that occurs in various spinous ligaments

↓

Calcification of supraspinous & interspinous ligaments – Dagger spine

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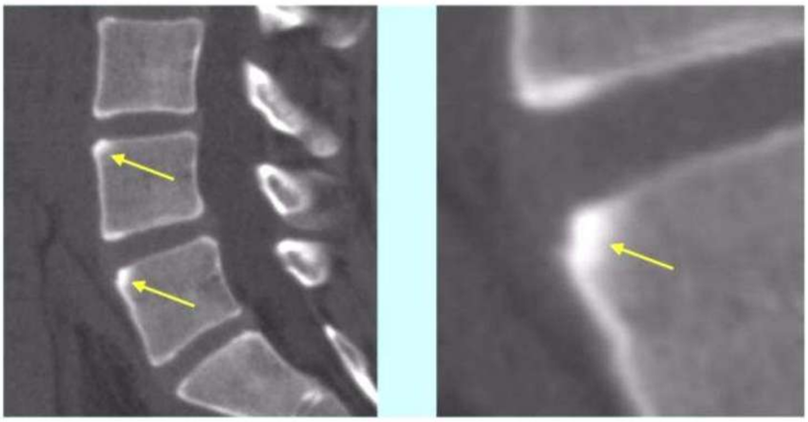

Shiny corner sign/Ramanus lesions Fig: 6

Reactive arthritis 00:31:53

- Sterile/non purulent arthritis
- Infection —1-4 weeks→ Arthritis
- Infection causing reactive arthritis
  ↓
  - Enteric infections (shigella, salmonella)
  - Urogenital (chlamydia)
  - URI

Clinical features

- 18-40 years
- M > F
- Asymmetrical additive mono/digoarthritis
- 30-50% chronicity

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Monoarthirits Fig: 7

Enthesitis Fig: 8

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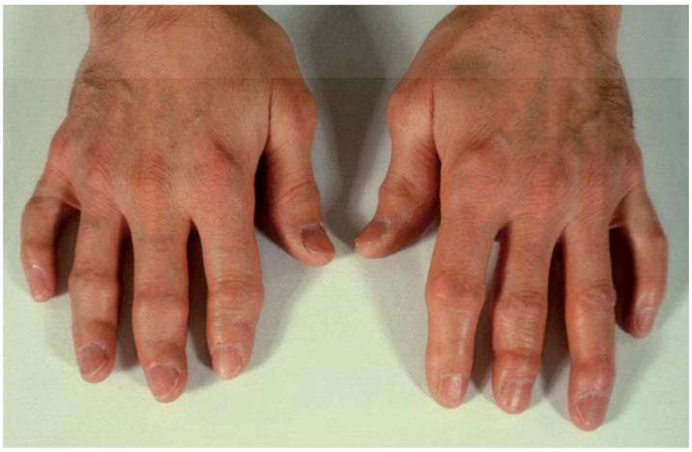

Dactylitis – Sausage digits Fig: 9

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Extra-skeletal manifestations

- Anterior uveitis
- Mucocutaneous manifestations
  - Keratoderma blennorrhagia
  - Circinate balanitis

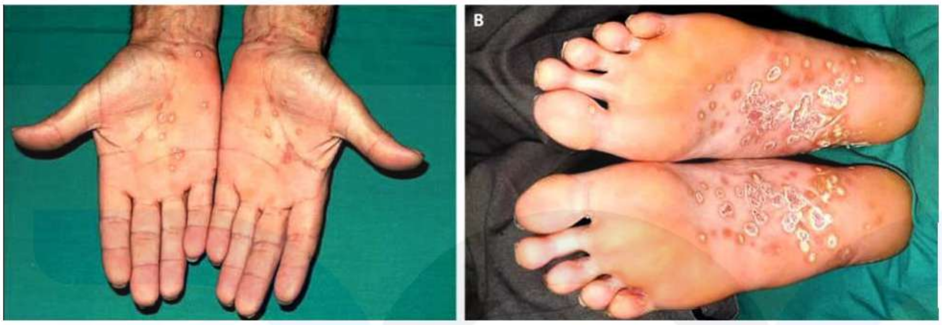


Fig: 10

Fig: 11

- Serpinginous ulcers which are painters over glans penis – Circinate balanitis

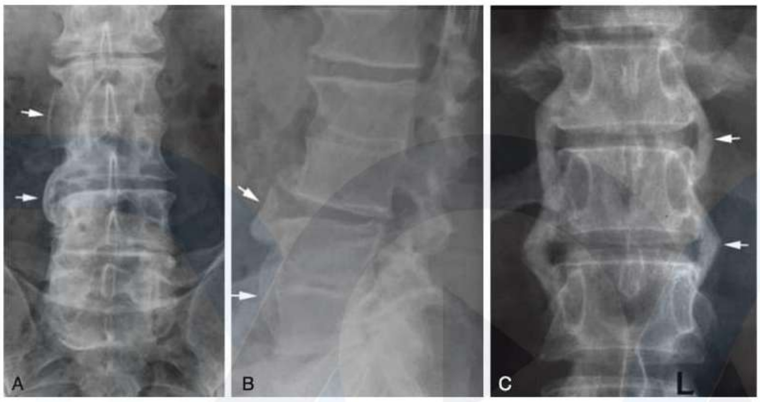
Reiter's syndrome

- Characteristic triad of
- Arthritis

- Urethritis
- Conjunctivitis

Diagnosis

- Clinical diagnosis
- Increase ESR, CRP



Syndermophytes – Non marginal Fig: 12

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	Ankylosing spondylitis	Reactive arthritis
Sacroiliitis	Bilateral, symmetric	Unilateral, asymmetric
Spondylitis	Bilateral, thin, marginal syndes	Asymmetric, non-marginal, "jug-handle" syndesmophyt

Treatment

- First choice – NSAID's – Indomethacin
- Antibiotics – only if the patient has concurrent infection

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- Steroids – monoarthritic → Intra articular steroids given
    - Topical steroids → keratoderma blennorrhagia circinate balanitis
- TNF α inhibitors

D/D

- Septic arthritis
- Crystal Associated Arthropathies (CAA)

    ↓
- Synovial fluid analysis

    ↓
- Septic arthritis LAA
    - Lot of neutrophilis
    - Polarised microscopy demonstrates crystals

Psoriatic arthritis 00:47:25

- 60-70% of cases → psoriasis → arthritis
- 20% → psoriasis + arthritis
- 20% → arthritis → psoriasis
- HLA B27 positive
    - HLA CW6 → psoriasis
    - HLA B57
    - HLA DR7
    - HLA DQ3

    (HLA B57, HLA DR7, HLA DQ3) – Associated with psoriatic arthritis

Skeletal manifestations

- Wright and moll classification

Clinical pattern on presentation	Percentage of patients
Asymmetrical oligoarthritis	50
Symmetrical polyarthritis	40
Distal interphalangeal arthritis	5
Arthritis mutilans	5
Spinal column involvement	40

- Most common pattern – asymmetrical oligoarthritis

Fig: 13

- D/P arthritis
- Dactylitis

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- Destructive form – arthritis mutilans

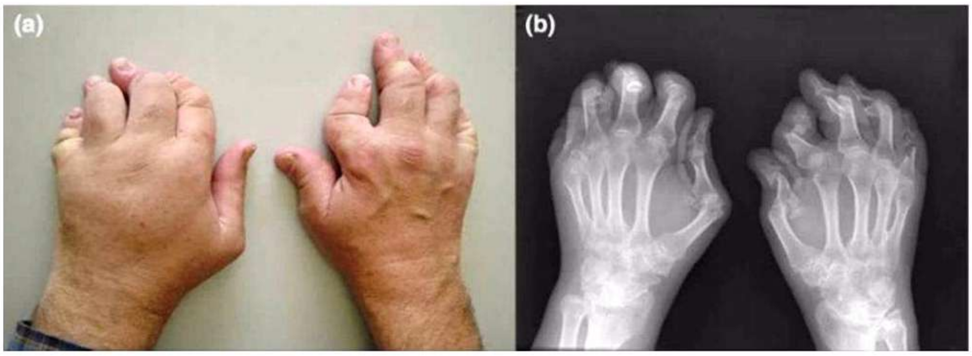
Fig: 14
Dactylitis associated with nail changes

Nail changes in psoriatic arthritis

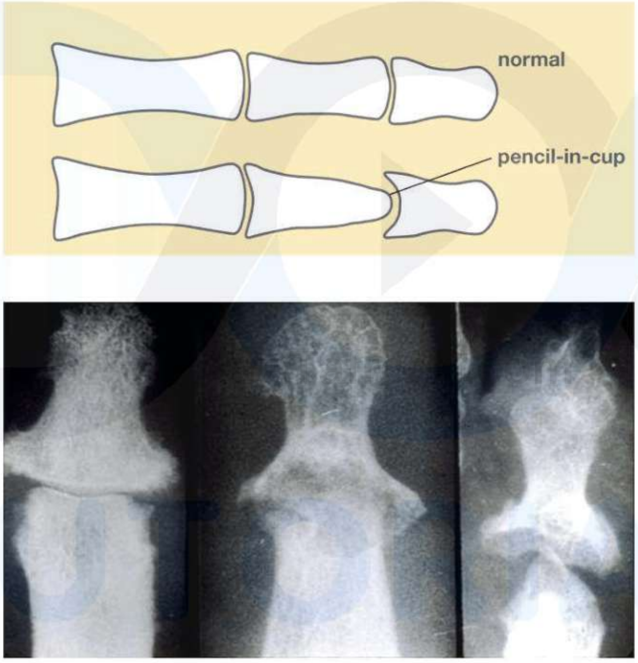
- Nail pitting
- Onycholysis
- Ridging of nails
- Yellowish colour changes
- Hyperkeratosis

Nail pitting Yellowish color
Fig: 15

change in nails



Arthritis mutilans Fig: 16



Pencil in cup deformity Fig: 17

Ivory phalanx Fig: 18

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Extra skeletal manifestations

- Uveitis
- Apical pulmonary fibrosis

Diagnosis

- CASPAR criteria
- To meet the CASPAR criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥3 points from any of the following five categories
  - Evidence of current psoriasis, [b,c] a personal history of psoriasis, or a family history of psoriasis
  - Typical psoriatic nail dystrophy observed on current physical examination
  - A negative test result for rheumatoid factor
  - Either current dactylitis[f] or a history of dactylitis recorded by a rheumatologist
  - Radiographic evidence of juxtaarticular new bone formation in the hand or foot

Treatment

- Psoriasis + Arthritis
- Anti TNF α inhibitors → DOC
- Methotrexate
- IL 17 monoclonal antibodies
  - Secukinumab
  - Ixekizumab

- Secukinumab

- IL 12/23 monoclonal
- JAK inhibitor – Tofacitinib
- PDE-4 inhibitor – Apremilast

Enteropathic arthritis 01:00:19

- Associated with chron's d/s > ulcerative colitis
- Most often presents as peripheral arthritis
- Treatment: TNF α inhibitors.

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CRYSTAL ASSOCIATED ARTHROPATHIES

Crystal Arthropathies

- Gout
- Pseudogout
- Calcium hydroxyapatite deposition disease
- Calcium oxalate deposition disease

Gout 00:01:40

- Middle aged males
- 40-60years
- Deposition of monosodium urate crystals (MSU)
- Uric acid → End product of purine metabolism
- Conditions predisposing gout

Nonmodifiable risk factors	Modifiable risk factors
Age Gender Ethnicity Genetic variants	Obesity Hypertension Hyperlipidemia Cardiovascular disease Diabetes mellitus Chronic kidney disease Dietary factors Alcohol Medications altering Urate balance

Diuretics

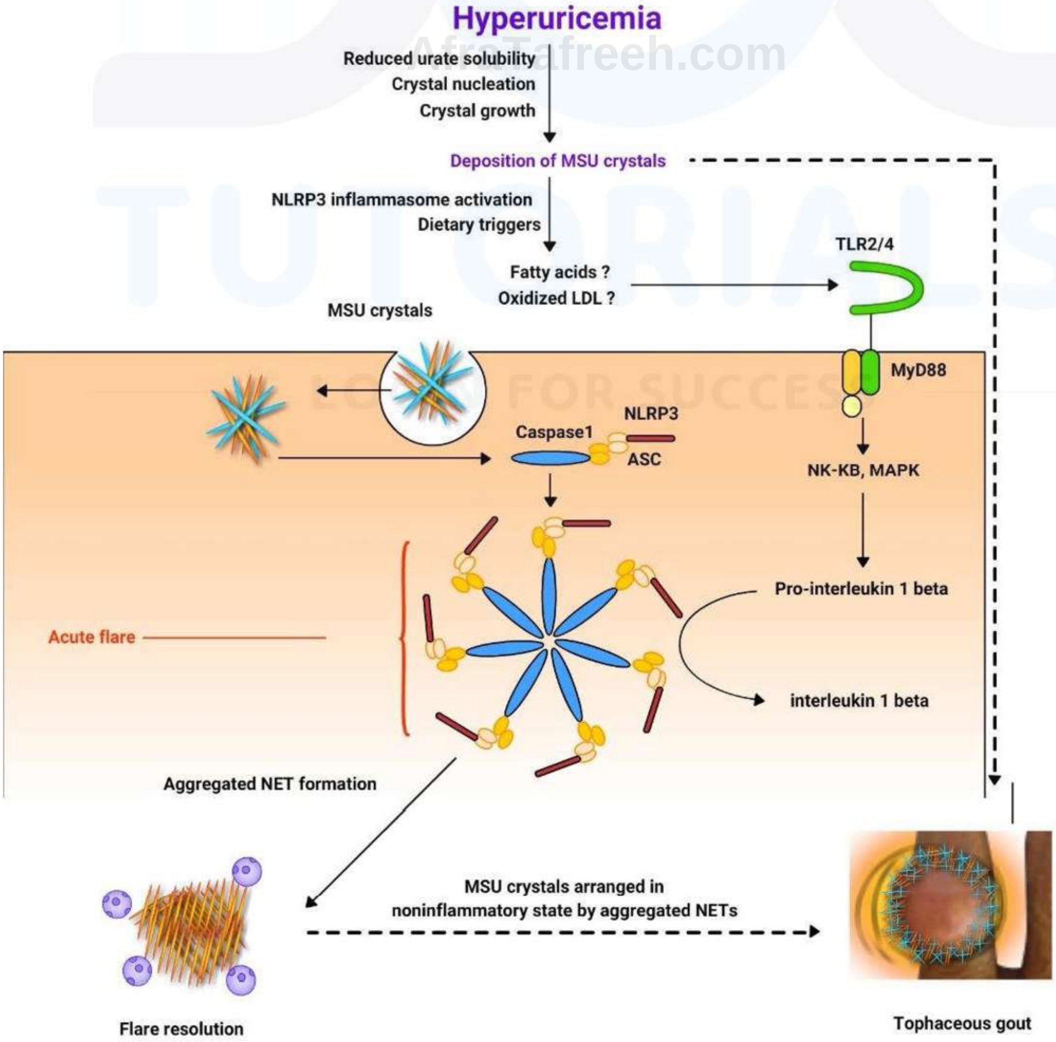
- Thiazide diuretics
- Loop diuretics

Organic acids

- Salicylates (Low dose)
- Nicotinic acid
- Pyrazinamide

Other

- Cyclosporine
- Ethambutol
- Ethanol
- Colony stimulating factors



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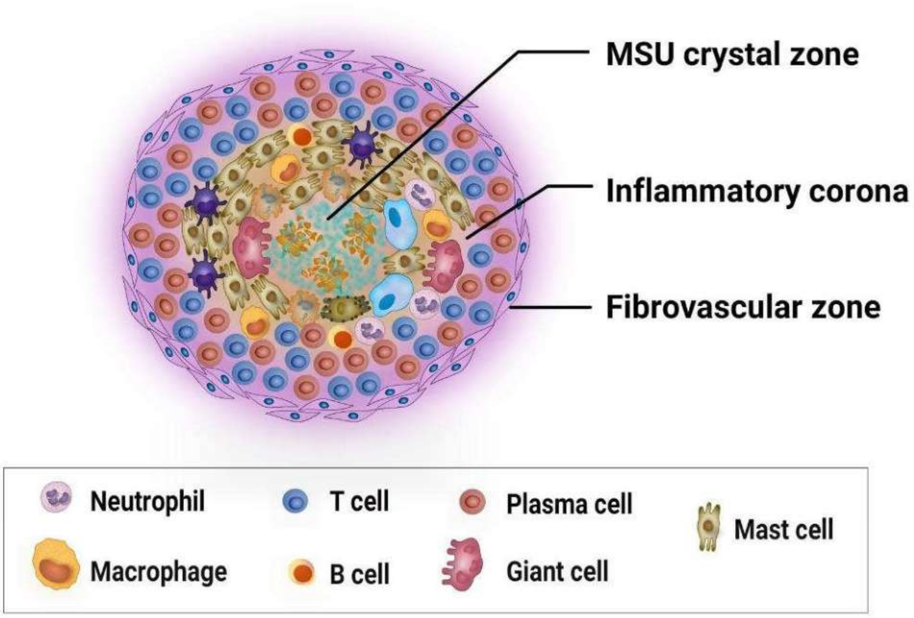

Clinical features

- Asymptomatic hyperuricemia
- Acute gouty arthritis
- Painful arthritis
- First joint involved – MTP point
- Pain
- Swelling
- Redness
- Tenderness
- Period between 2 episodes is called inter critical gout
- Asymptotic hyperuricemia may predispose to coronary & cerebrovascular accident risk because it is related both directly to insulin resistance
- Metabolic syndrome profile

Inflamed tophaceous gout

Fig: 1

Tophus of knee joint

Fig: 2

Martel's sign

Fig: 3

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Tophi deposition over prepatellar area

Fig: 3

Renal problems

- Urate nephropathy – Predominant attack over tubulo-Interstitum
- Increased risk of nephrolithiasis

Investigations

- Joint aspiration – Synovial fluid study
- Normal synovial cell <200 cells/ML
- In gout – cell count would be elevated (3000-6000 cells/μL)
- Demonstration of MSU crystals by polarizing microscopy

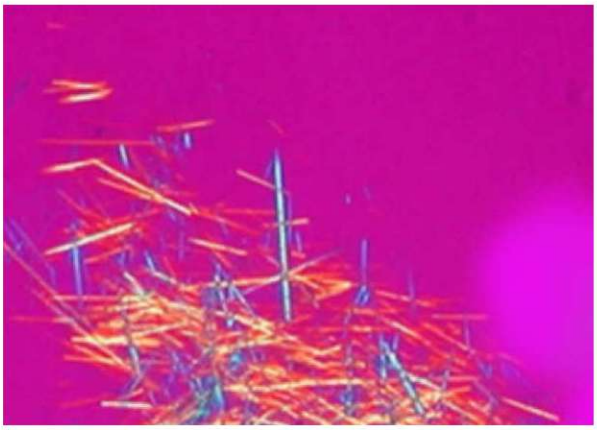

Fig: 4

- Negatively birefringent needle shaped crystals
- S. urine acid normal
- X-ray – erosive arthritis
- Martel's sign
- USG – Double contour sign
- LFT
- RFT
- Fasting lipid profile

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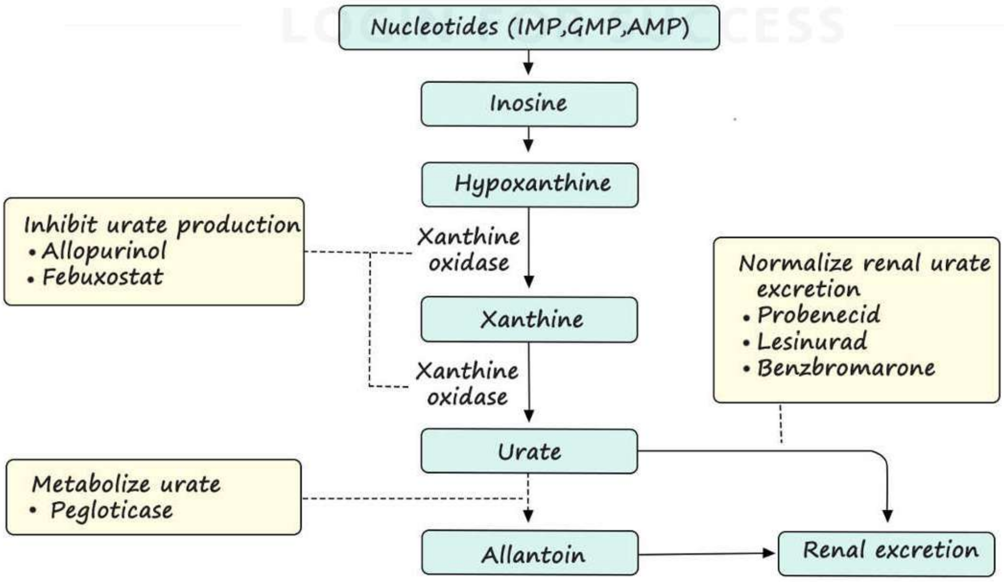
Treatment



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- Acute gouty arthritis
- Chronic gout

Acute gouty arthritis

- NSAID's – Ibuprofen & Naproxen
- Colchicine: 0.6mg Tial

  ↓

  Side effects diarrhea
- Steroids: Oral steroids intro-articular
- Allopurinol
- Not to be given in acute gouty arthritis because allopurinol will be decreased uric acid production → Flore up of episodes

Chronic gout

- Hyperuricemia >6.8mg%
- Target is lower uric level <6mg%
- Individuals with HLAB 5801 have risk of developing stevens Johnson syndrome
- Bone marrow suppression
- Hepatoxicity
- CKD-Renal dose modification required
- Febuxostat
- No dose reduction in CKD
- Withdrawn in case of CVA
- Uricosuric drugs – Probenecid

- 24hrs urinary uric acid levels → Less in spite of hyperuricemia → Problem in uric acid excretion
- Rx of metabolic syndrome

Pseudogout 00:40:14

- Also known as CPPD – Calcium pyrophosphate deposition disease
- Most common in elderly males
- May be asymptomatic acute subacute or chronic

↓

Can mimic gouty arthritis

Conditions associated with calcium pyrophosphate crystal deposition disease

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- Aging
- Disease associated
- Primary hyperparathyroidism
- Hemochromatosis
- Hypophosphatasia
- Hypomagnesemia
- Chronic gout
- Post meniscectomy
- Gitelman's syndrome
- Epiphyseal dysplasia's
- Commonest joint – Knee

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Chondrocalcinosis Fig: 5

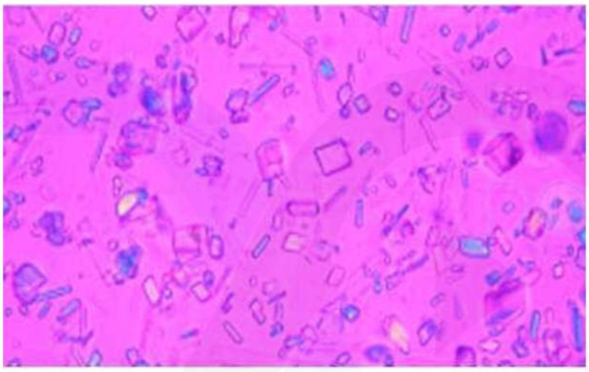

Fig: 6
Weak positive birefringent rhomboid crystals

Treatment

- NSAIDS
- Steroids

Calcium hydroxyapatite deposition disease 00:45:17

- Extremely destructive arthropathy

Fig: 7

- Most common shoulder joints
- Joint fluid aspiration – requires electron microscopy for demonstration of crystals

Fig: 8

Calcium oxalate deposition diseases 00:47:47

- Associated with CKD

Bipyramidal shaped crystals Fig: 9

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VASCULITIS

- Vessel wall inflammation

Classification 00:01:46

- Revised international chapel hill consensus conference classification

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SPECIAL ARTICLE

2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides

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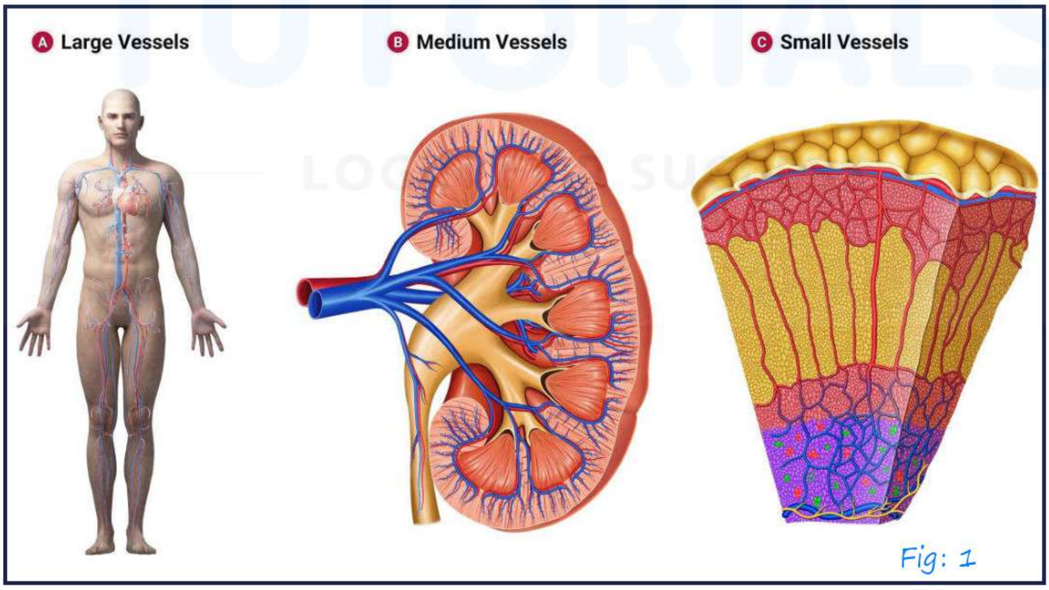


Fig: 1

- Divided into
  - Large vessel vasculitis – Aorta and its branches

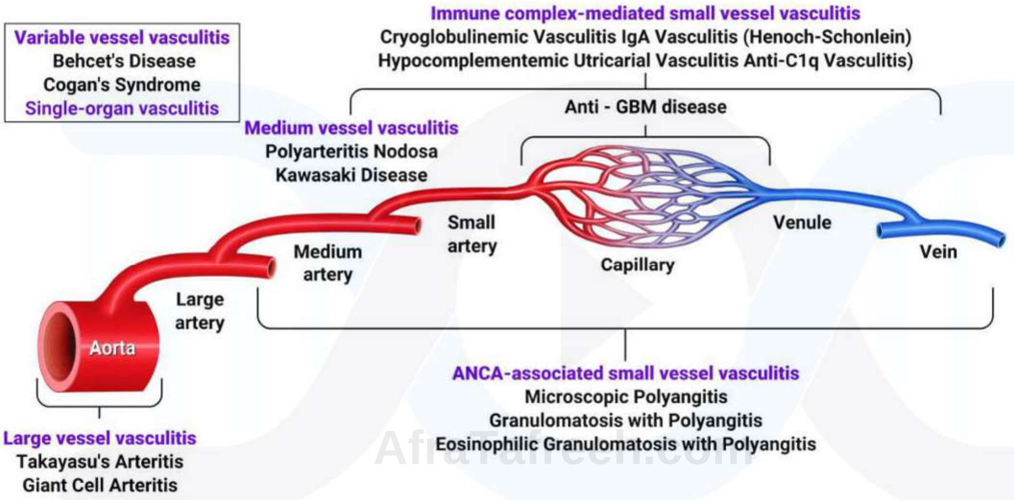
- Medium vessel vasculitis – Visceral with, veins and initial branches
- Small vessel vasculitis - Intraparenchymal

  Arteries

  Arterioles

  Venules

  Veins, capillaries



1.Large vessel vasculitis

- Giant cell arteritis
- Takayasu arteritis

2.Medium vessel vasculitis

- Polyarteritis nodosa
- Kawasaki disease

3.Small vessel vasculitis

- ANCA associated vasculitis (AAV)
- Immune complex mediated vasculitis
- Antineutrophil cytoplasmic antibody
  - P - ANCA → perinuclear
  - C - ANCA → cytoplasmic

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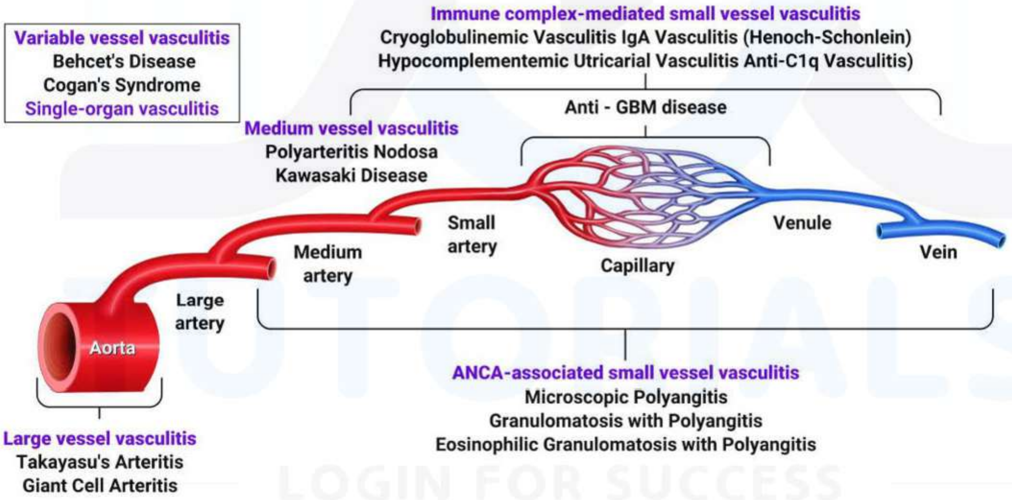
- Microscopic polyangiitis
- Granulomatosis with polyangiitis (GPA) – Wegener's granulomatosis
- Eosinophilic granulomatosis with polyangiitis (EGPA) - Churg sters vasculitis
- Immune complex mediated vasculitis
  - Cryoglobinemic vasculitis
  - Good posture syndrome
  - Henoch schonlein vasculitis
  - Hypocomplimentemic vasculitis



- Variable vessel vasculitis
  - Behcet's disease
  - Cogant syndrome
- Single organ vasculitis
  - 1° angiitis of CNS
  - 1° CNS vasculitis

Vasculitis syndrome	
Primary Vasculitis Syndromes	secondary vasculitis Syndromes
Granulomatosis with polyangiitis (Wegener's) Microscopic polyangiitis Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) cryoglobulinemic vasculitis IgA vasculitis (Henoch-Schönlein) Cryoglobulinemic vasculitis Polyarteritis nodosa Kawasaki disease Giant cell arteritis Takayasu arteritis Behçet's disease Cogan's syndrome Single-organ vasculitis Cutaneous leukocytoclastic angiitis Cutaneous arteritis Primary central nervous system vasculitis Isolated aortitis	Vasculitis associated with probable etiology Hepatitis C virus-associated Hepatitis B virus-associated vasculitis Cancer-associated vasculitis Vasculitis associated with systemic disease Lupus vasculitis Rheumatoid vasculitis Sarcoid vasculitis

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Giant cell arteritis 00:16:09

- Elderly population
- Age > 50 years
- F > M
- Other names
  - Cranial arteritis

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- Temporal arteritis
- Granulomatous arteritis (not used now)

- Etiopathogenesis
  - HLA DR_4 association
  - Pan-arteritis
  - Disease is initiated in tunica adventitia

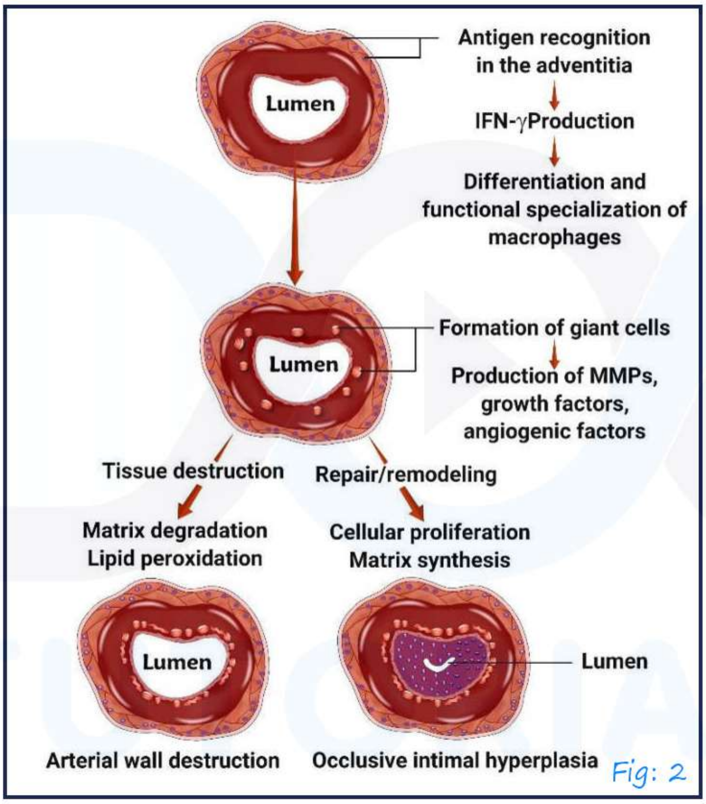

Fig: 2

- Clinical features
  - Most common → headache
  - Jaw claudication
  - Fatigue, myalgia
  - Fever – PUO
  - Polymyalgia rheumatica (40-50%) → stiffners involving neck, shoulder, lower back, hips and thighs
  - Visual loos – due to AION (Anterior ischemic optic neuropathy)

- Pure aortic involvement – 25% GCA
- Temporal arteritis

↓

Superficial temporal artery

- dilated and tortuous
- tender on palpitation

Fig: 3

Symptom	Frequency (%)
Headache	76
Weight loss	43
Fever	42
Fatigue	39
Any visual symptom	37
Anorexia	35
Jaw claudication	34
Arthalgia	30
Unilateral visual loss	24
Bilateral visual leoss	15
Vertigo	11
Diplopia	9

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- AION → Altitudinal visual defect

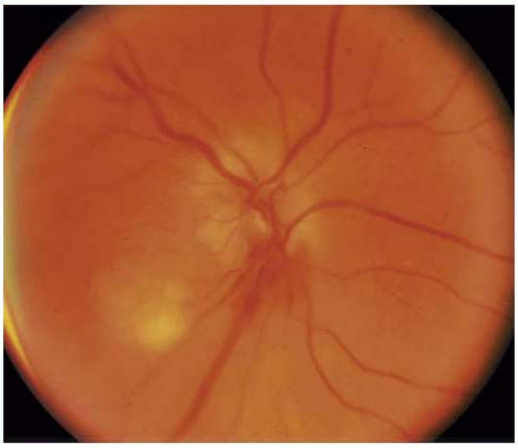

Fig: 4

- Scalp tenderers ⊕

- Investigations
  - ESR increase > 100
  - Ultrasound duplex scan – halo sign
  - IOC: - biopsy

American college of rheumatology classification criteria for giant cell arteritis	
Criterion	Definition
Age at disease on set ≥ 50yr	Development of symptoms or findings beginning at age 50yr or older
New headache	New onset or new type of localized pain in the head
Temporal artery abnormality	Temporal artery tenderness to palpation or decreased pulsation unrelated to arteriosclerosis of cervical arteries
Elevated ESR	ESR ≥50mm/hr by the Westergren method
Abnormal artery biopsy	Biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation usually with multinucleated giant cells
For purpose of classification a patient with vasculitis is said to have giant cell (Temporal) Arteritis if at least three five criteria are present. The presence of any three or more criteria yields a sensitivity of 93.5% and a specificity of 91.2%	

- Chance of skip lesions in giant cell arteritis

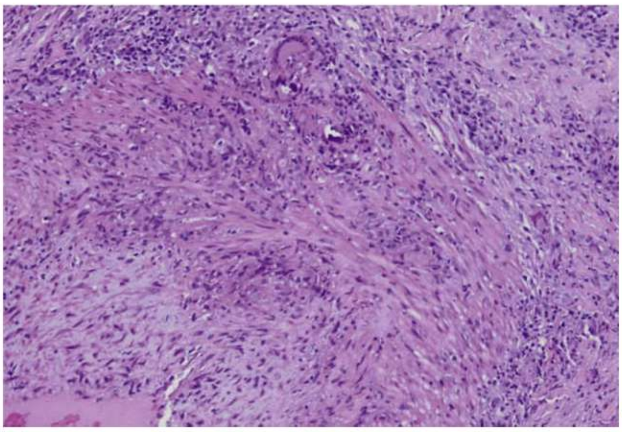

Fig: 5

- Duplex ultrasound → Halo sign

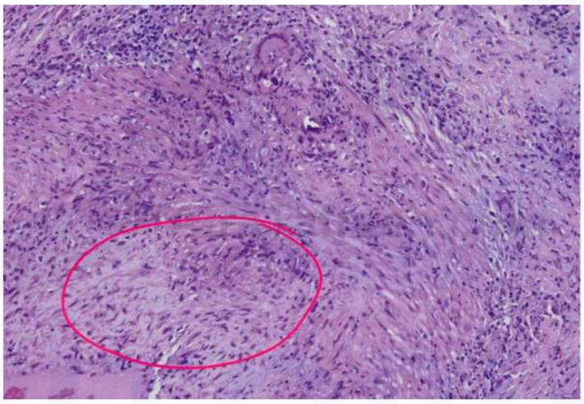

Fig: 6

- Management

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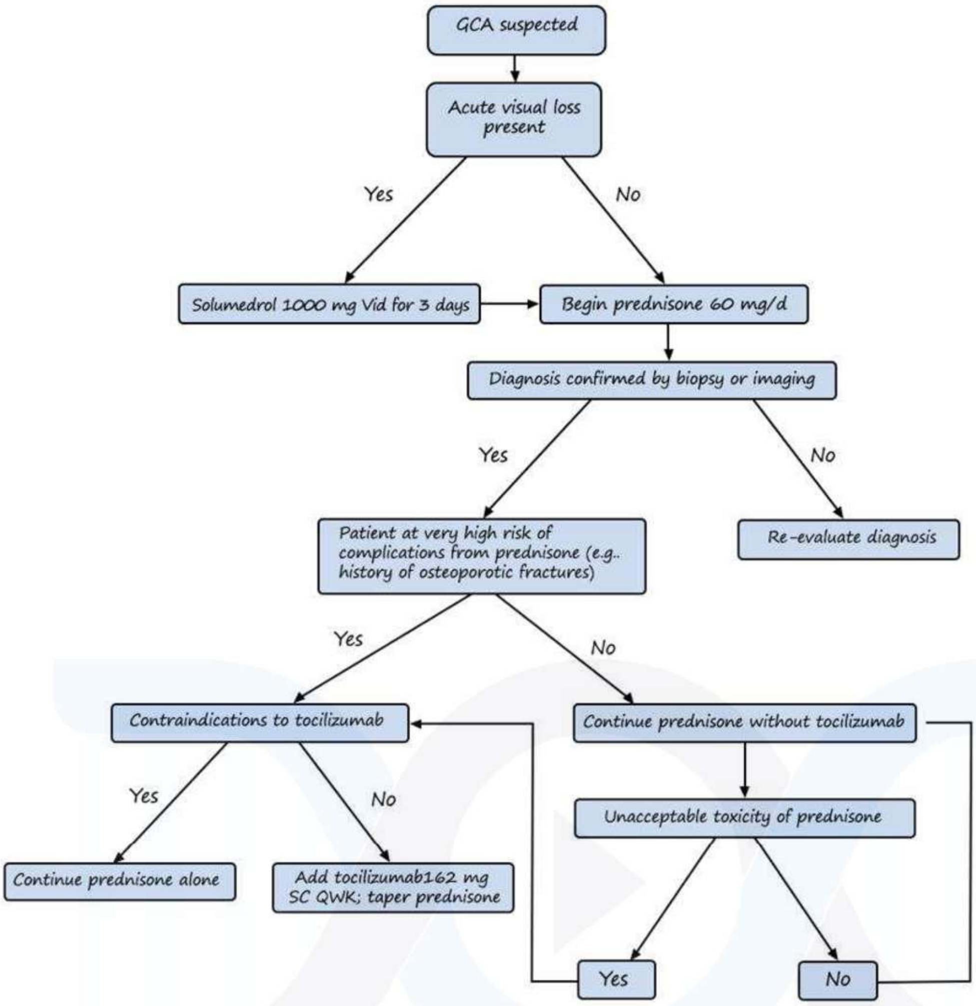

- Tocilizumab – 2017 FDA approved

Takayasu arteritis 00:40:25

- Young – middle aged females
- Also referred to as aortic areh syndrome and nonspecific aorto arteritis

Frequency of arteriographic abnormalities and potential clinical manifestations of arterial involvement		
Artery	Percentage of arteriographic abnormalities	Potential clinical manifestation
subclavian	93	Arm claudication, Raynaud's phenomenon
Common carotid	58	Visual changes, Syncope transient ischemic attacks, stroke
Abdominal aorta	47	Abdominal pain, Nausea, vomiting
Renal	38	Hypertension, renal failure
Aortic arch or root	35	Aortic insufficiency congestive heart failure
Vertebral	35	Visual changes dizziness
Coeliac axis	18	Abdominal pain, nausea, vomiting
Superior mesenteric	18	Abdominal pain nausea vomiting
Iliac	17	Leg claudication
Pulmonary	10-40	Atypical chest pain, dyspnea
Coronary	<10	Chest pain, myocardial infarction

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American college of rheumatology classification criteria for Takayasu's arteritis

- Onset before age 40yr
- Limb claudication

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- Decreased branchial artery pulse
- Unequal arm blood pressure (>10mm Hg)
- Subclavian or aortic bruit
- Angiographic evidence of narrowing or occlusion of aorta or its primary branches or large limb arteritis

Treatment

- Steroids
- Tocilizumab
- Angioplasty

Comparison of giant cell arteritis and Takayasu's arteritis		
Feature	Giant cell arteritis	Takayasu's arteritis
Female-male ratio	2:1	8:1
Age range	≥50yr	<40yr
Average age of onset	72yr	25yr
Visual loss	10%-30%	Rare
Involvement of aorta or its major branches	Granulomatous arteritis	Granulomatous arteritis
Pulmonary artery involvement	No	Occasionally
Renal hypertension	Rare	Common
Claudication	Uncommon	Common
Ethnic groups with highest incidence	Scandinavian	Asian
Corticosteroid responsive	Yes	Yes
Bruits present	Minority	Majority
Surgical intervention needed	Rare	Common

Polyarteritis nodosa 00:53:10

- Medium vessel vasculitis
- Age: - 50 – 60 years
- No granuloma formation
- No pulmonary vessel involvement (but bronchial vessel may be involved)
- No glomerulonephritis (but renal artery involved)
- No ANCA association
- Clinical features: -

Clinical manifestations related to organ system involvement in polyarteritis nodosa		
Organ system	Percent incidence	Clinical manifestations
Renal	60	Renal failure, hypertension
Musculoskeletal	64	Arthritis, arthralgia, myalgia
Peripheral nervous system	51	Peripheral neuropathy mononeuritis multiplex
Gastrointestinal tract	44	Abdominal pain, nausea and vomiting bleeding bowel infraction and perforation cholecystitis hepatic infraction pancreatic infraction
Skin	43	Rash, purpura, nodules cutaneous infracts, livedo reticularis Raynaud's phenomenon
Cardiac	36	Congestive heart failure myocardial infraction, pericarditis
Genitourinary	25	Testicular, ovarian or epididymal pain
Central nervous system	23	Cerebral vascular accident altered mental status seizure

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- Associated with Hep. B infection (30%)
- Associated with hairy cell leukemia
- Inv: - angiogram → multiple micro-aneurysms

Fig: 7

American college of rheumatology criteria for classification of polyarteritis nodosa

- Weight loss ≥4kg
- Livedo reticularis
- Testicular pain or tenderness
- Myalgias weakness or leg tenderness
- Mononeuropathy or polyneuropathy
- Diastolic blood pressure >90mm Hg
- Elevated blood urea nitrogen or creatine levels
- Hepatitis B virus
- Arteriographic abnormality
- Biopsy of a small or medium sized artery containing polymorphonuclear neutrophils
- Treatment PAN: - steroids + cyclophosphamide

- Small vessel vasculitis
  - ANCA associated vasculitis
  - Immune complex mediated vasculitis

ANCA vasculitis

P – ANCA
↓
- Against myeloperoxidase
- Myeloperoxidase is a2urophillic granules in monocytes and neutrophils

C – ANCA
↓
- Against proteinase – 3
- Proteinase 3 is present in granules of neutrophils

i. GPA
ii. Microscopic polyangiitis
iii. EGPA
iv. Renal limited vasculitis

} Necrotizing vasculitis

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Sensitivity of Anti-PR3 and anti-MPO antibodies			
Antibody sensitivity			
Disease entity	Anti-PR3	Anti-MPO	Negative ANCA
Granulomatosis with polyangiitis (Generalized)	80-90	0-10	10
Microscopic polyangiitis	10-20	60-70	10-15
Renal limited vasculitis pauci-immune glomerulonephritis	20	64	15-20
Eosinophilic granulomatosis with polyangiitis	10	50	35-50

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Granulomatosis with polyangiitis 01:09:01

- Wegener's granulomatosis
- Necrotizing granulomatosis vasculitis
- Age: - 40-50 years
- M: F
- Involves
  - upper respiratory tract (most common)
  - lower respiratory tract
  - kidneys respiratory tract
  - eye respiratory tract
  - skin respiratory tract
  - CNS respiratory tract

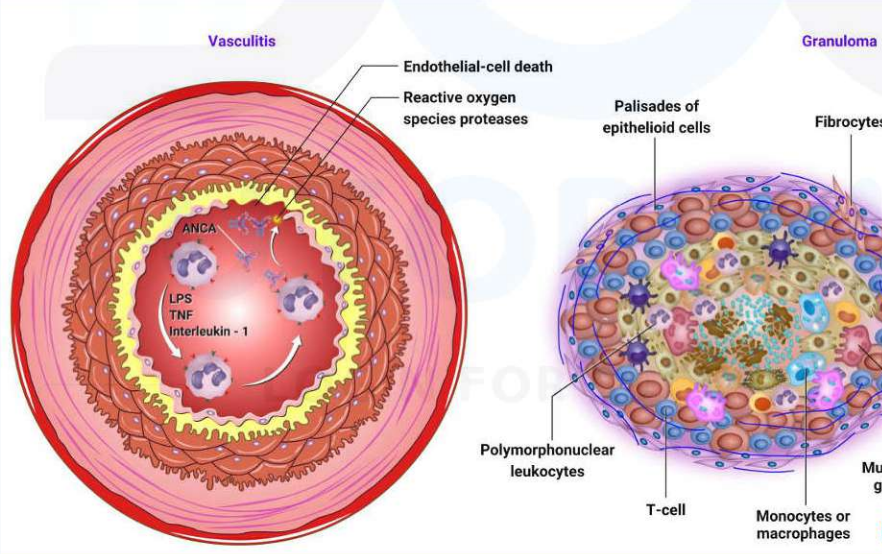

Fig: 8

- Pathology: - vasculitis + granuloma
  - Nrcrotising granuloma

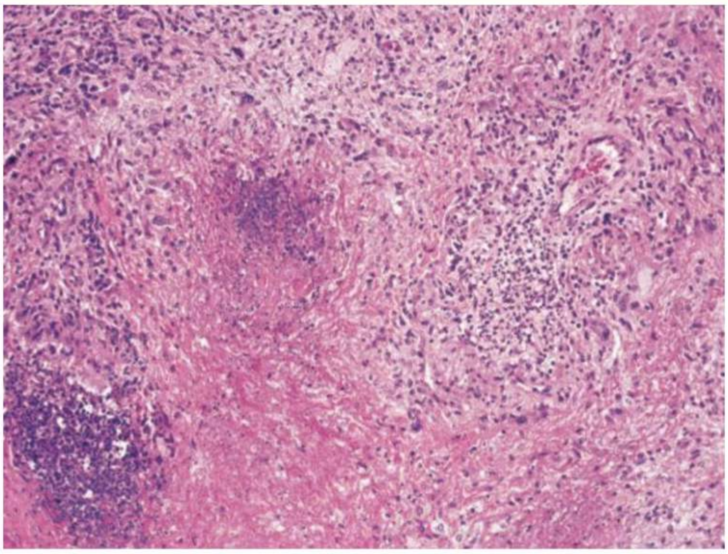

Fig: 9

- Upper respiratory tract involvement
  - Sinusitis
  - Serous otitis media
  - Nasal septal involvement (saddle nose deformity)
  - Subglottic stenosis
  - High recurrence of granulomatosis with chronic nasal carriage of staphylococcus
- Lower respiratory tract
  - Pulmonary nodules

    Cavities

    Infiltrates
  - Alveolar hemorrhage
  - Cough
  - Dyspnea
  - hemoptysis
- Kidney involvement
  - Glomerulonephritis

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- Proteinuria
- Hematuria
- RBC casts
  - RPGN
  - Renal failure
- Eyes – conjunctivitis, episcleritis, scleritis
- Skin – purpura
- PNS – Peripheral neuropathy
- CNS –

Granulomatosis with polyangiitis (Wegener's): Frequency of clinical manifestations in 158 patients studied at the national institutes of health		
Manifestation	Percentage at disease onset	Percentage throughout course of disease
Kidney		
Glomerulonephritis	18	77
Ear/Nose/throat	73	92
Sinusitis	51	85
Nasal disease	36	68
Otitis media	25	44
Hearing loss	14	42
Subglottic stenosis	1	16
Ear pain	9	14
Oral lesion	3	10
Lung	45	85
Pulmonary infiltrates	25	66
Pulmonary nodules	24	58
Hemoptysis	12	30
Pleuritis	10	25

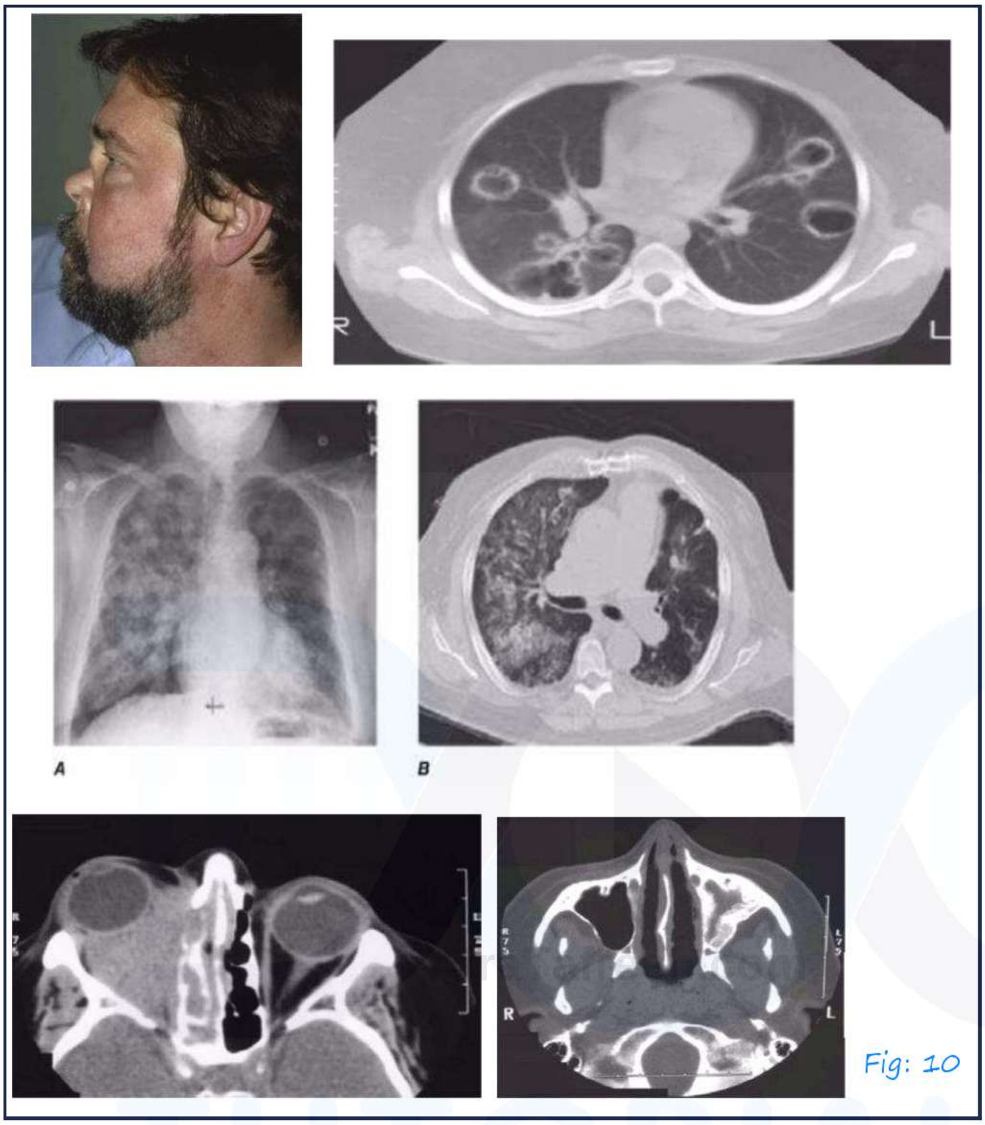

Fig: 10

- Highest diagnostic yield is with lung biopsy.

Microscopic polyangiitis 01:21:47

- Age: 45-55 years
- M>F
- Necrotizing vasculitis without granuloma
- Clinical: -
  - Renal → RPGN
  - Cutaneous → purpura
  - Lung → diffuse alveolar hemorrhage

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Eosinophilic granulomatous polyangiitis 01:27:47

- Churg straurs syndrome
- Necrotizing vasculitis associated with granulomas
- F > M
- Age: - 40 – 50 years
- Characterized by
  - asthma
  - tissue and blood eosinophilia
  - extravascular granulomas
  - vasculitis of multiple organ systems
- clinical feature: - Asthma with pulmonary infiltrates

  eosinophil > 1000/μL

Fig: 11

- vasculitis skin rashes, purpura
- myocardium – most common cause of mortality

Clinical features of polyarteritis nodosa (PAN), MPA, and GPA			
Clinical features	PAN	MPA	GPA
Kidney involvement			
Renal vasculitis with infracts and microaneurysms	Yes	No	No
Rapidly progressive glomerulonephritis with crescents	No	Yes	Yes
Lung involvement			
Alveolar hemorrhage	No	Yes	Yes
Laboratory data			
Hepatitis B virus infection	Yes	No	No
P-ANCA	<10%	50%-80%	10%-20%
Abnormal angiogram with microaneurysms	Yes	No	No
Histology	Necrotizing vasculitis	Necrotizing vasculitis (No granulomas)	Granulomatous vasculitis
Relapses	Rare	Common	Common

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Treatment of ANCA associated vasculitis

- steroids
- steroids + cyclophosphamide
- mepolizumab → monoclonal antibody against IL – 5
- IL-5- most potent eosinophil activating cytokine

↓

Can be used for churg straws vasculitis

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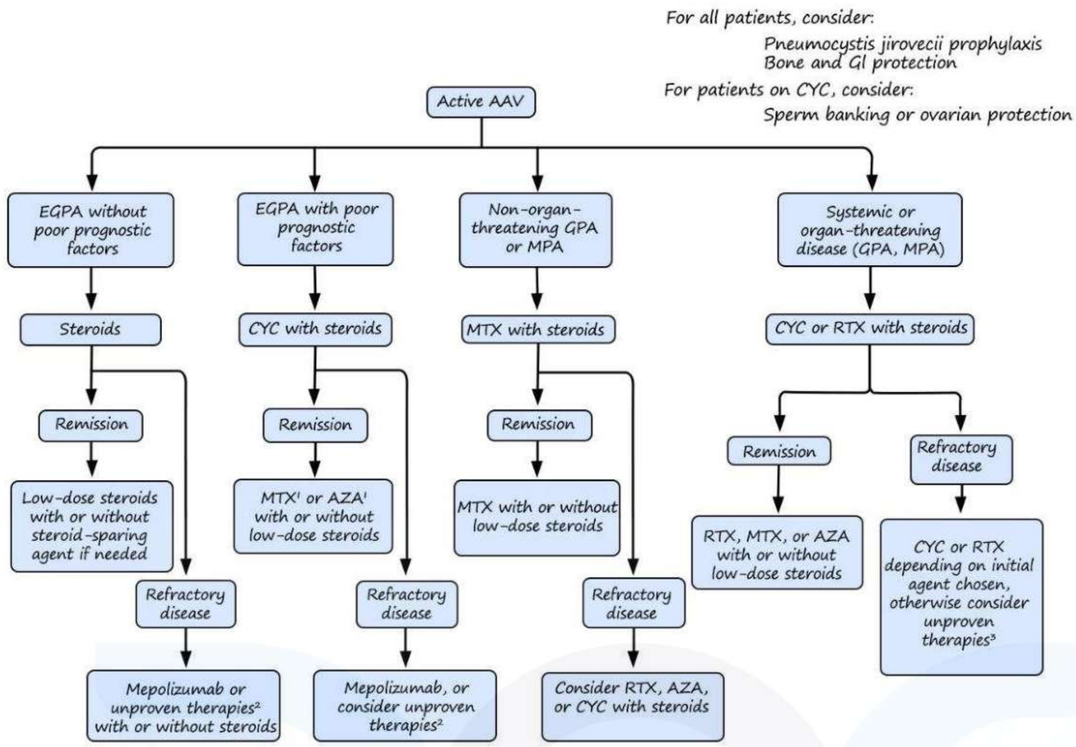

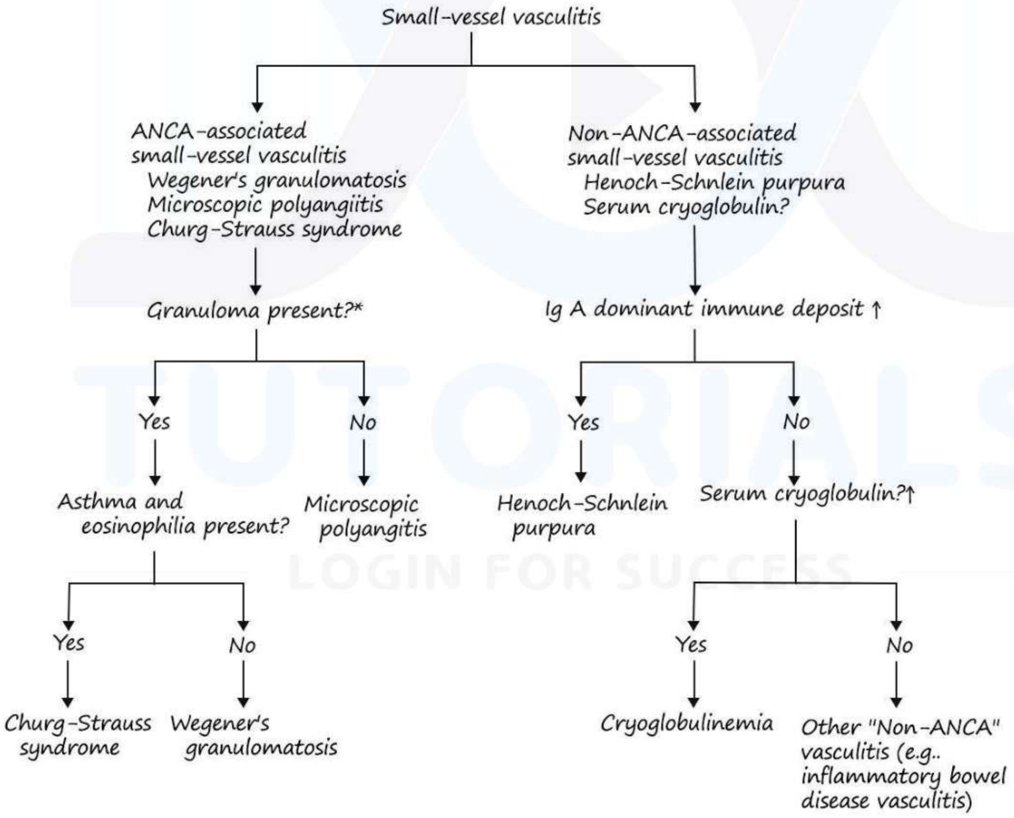

Immune complex mediated vasculitis

- Ig A vasculitis (Henoch schontein purpura)
- Good posture syndrome
- Cryoglobulinemic vasculitis
- Cutaneous leukocytoclastic vasculitis

IgA Vasculitis 01:46:46

- Age: - 4-T years
- M>F
- Clinical features: -
  - Palpable, non-thrombocytopenic purpura

    ↓

    Butiocks, extensor aspect

Fig: 11

  - G.I symptoms (70%)
- Nausea
- Vomiting
- Colicky abdominal pain → bowel angina
- Blood and mucus in stools
- Constipation
- Diarrhea
  - Renal → Glomerulonephritis
  - Arthralgia/arthritis

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American college rheumatology 1990 criteria for the classification of Henoch-schonlein purpura (IgA vasculitis)

- Palpable purpura
- Age at onset <20years
- Bowel angina
- Vessel wall granulocytes on biopsy

- Skin biopsy – leucocytoclastic vasculitis
- Treatment: - steroids → 1mg/kg/day

Cryoglobulinemic vasculitis 01:53:17

- Cryoglobulins are cold precipitable immune globulins which can either be monoclonal / polyclonal
- Also known as essential mixed cryoglobulinemia

Types of cryoglobulins			
Cryoglobulin	RF positivity	Monoclonality	Associated disease
Type I	No	Yes (IgG or IgM)	Hematopoietic malignancy (multiple myeloma, Waldenstron's Macroglobulinbemia)
Type II	Yes	Yes (polyclonal IgG, Monoclonal IgM)	Hepatitis C other infection sjogren's syndrome SLE
Type III	Yes	No (polyclonal IgG and IgM)	Hepatitis C other infection sjogren's syndrome SLE

- Clinical features:
  - Palpable purpura

- Renal → membranoproliferative glomerulonephritis
- Arthritis/arthralgia
- Weakness
- Peripheral neuropathy

- Treatment: -
  - Antiviral
  - Rituximab
  - Steroids

Variable vessel vasculitis

- Behcets disease
- Cogan's syndrome

Behcet's diseases 01:59:37

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- Multisystem disorder
- Oral and genital ulcer
- Ocular involvement → ureitis episcleritis / scleritis
- CNS involvement →
  - neurobehcet's disease
  - brainstem involvement
- Superficial thrombophlebitis
- Deep venous thromobosis

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Clinical manifestations of Behcet's disease		
Mucocutaneous	Oral aphthae	86%-100%
	Genital aphthae	57%-93%
	Extra-Genital aphthae	3%-6%
	Erythema nodosum – Like lesions	15% - 78%
	Papulopustular lesions	30% - 96%
Ocular	Anterior/posterior uveitis, Pan uveitis, Iridocyclitis, Keratitis, Episcleritis, Vitritis, Optic neuritis, Retinal vein occlusion	40-60%
Vascular	Superficial thrombophlebitis deep vein thrombosis	30-40%
	Arterial aneurysm	3%-12%
Neurologic	CNS involvement peripheral nervous system involvement	3% - 25%
Gastrointestinal	Chronic diarrhea mucosal ulceration	3%-26%
Musculoskeletal	Arthritis arthralgia	45%-60%

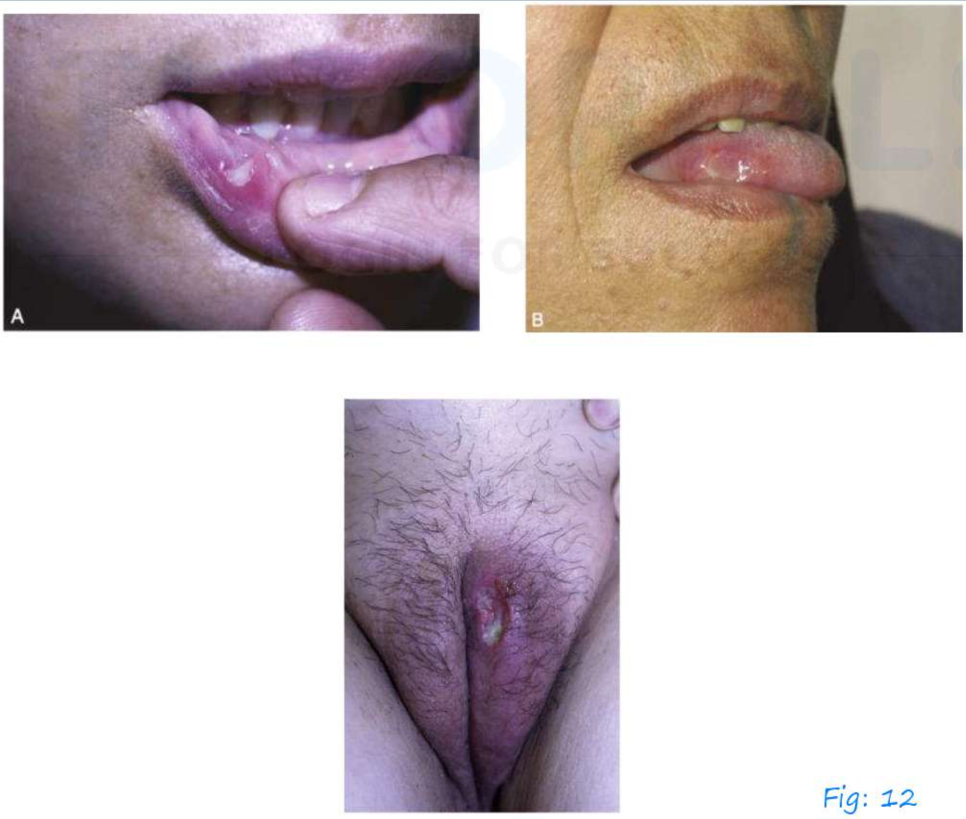

Fig: 12

- Pathergy test: - blunt hypodermi needle is inserted into the skin at

An angle of 30° tangentially (4 pricks)

↓

Reading taken after 24-48 hours

↓

Papule/ pustule formation

Fig: 13

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- Diagnosis: -

International criteria for Behcet's disease
Diagnosis established by score ≥4
Two points each • Oral aphthosis • Genital aphthosis • Ocular lesions
One point each • Skin lesions • Neurologic manifestations • Vascular manifestations • Positive pathergy test

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- Combination of auto inflammatory and autoimmune disorder
- Pathology
  - Perivasculitis
  - Early neutrophil infiltration
  - Endothelial swelling
- Antibodies
  - Anti-saccharomyces cervisea antibodies
  - Antibodies to selenium binding protein
  - Antibodies to enolase → endothelial cells
- Treatment: -
  - Mucocutaneous manifestations – topical steroids
  - Mucocutaneous + arthritis → colchicine
  - Uveitis and neuro Behcet' s → systemic steroids
  - Pulmonary aneurysms: - cyclophosphamide

Cogan's syndrome 02:10:56

- Interstitial keratitis
- Audio vestibular symptoms (vertigo).

INFLAMMATORY MYOPATHIES

Introduction 00:00:26

Immune mediated myopathies

- Also referred to as inflammatory myopathies

Common features

- Muscle weakness
- Raised creatinine kinase
- Inflammatory muscle biopsy

Entetities

- Dermatomyositis
- Polymyositis
- Immune Mediated Necrotising Myopathy (IMNM)
- Anti-synthetase syndrome
- Overlap syndrome
- Inclusion body myositis

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Dermatomyositis 00:03:29

- Most common inflammatory myopathy
- Can affect all ages
- Clinical features:
  - Acute to subacute symptoms
  - Symmetric proximal muscle weakness
  - Neck weakness
  - Extra-ocular m/s spared

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- Facial muscles are usually
- spared

- Associated cutaneous features

Fig: 1

Violaceous red rash over periorbital region

↓

Heliotrope rash

Photosensitive rash

Fig: 2

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Rash in anterior aspect of neck

↓

V sign

Fig: 3

Rash over neck and upper back

↓

Shawl sign

Fig: 4

Rashes + scaling over MCP, proximal & distal IP joints

↓

Gottron's papule

Mechanics hands Fig: 5

Periungual telangiectasias

Fig: 6

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Calcinosis cutis → more likely to occur in juvenile dermatomyositis Fig: 7

Antibodies and their clinical relevance

Myositis-specific antibodies (Based on subtype of myositis)	Characteristic clinical features
Dermatomyositis Anti-Mi-2	Classical skin rash, moderate muscle involvement, favourable response to immunotherapy
Anti-TIF-ty	Strong associated with cancer, severe skin rash, hypo-pigmented red on white patches, variable degree of muscle involvement
Anti-NXP-2	Increased risk of malignancy, classic skin, rash, mild-to-moderate muscle involvement, subcutaneous

	calcifications, peripheral oedema
Anti-MDA-5	Severe skin rash, no/minimal muscle involvement, skin ulcerations, rapidly progressive interstitial lung disease
Anti-SAE	Classic rash, mild muscle involvement, dysphagia

Fig: 8

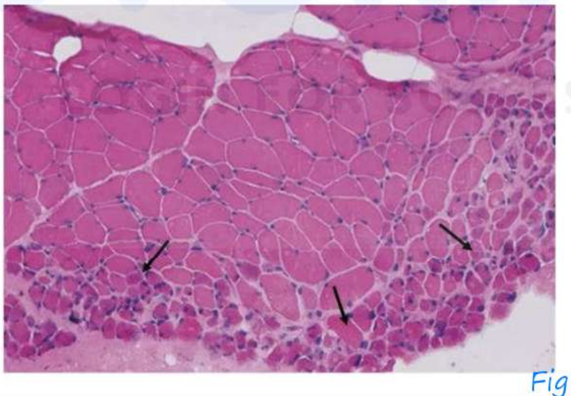

Fig: 9

Muscle biopsy

↓

Perifascicular atrophy

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- Immunohistochemistry → Increase expression of human mycovirus resistance protein-1

Polymyositis 00:15:40

- Diagnosis of exclusion
- <5%
- Clinical features
  - Similar to dermatomyositis
  - Symmetric proximal muscle weakness
  - Neck weakness
  - Pharyngeal weakness

Immune mediated necrotizing myopathy 00:16:52

Anti- signal recognition particle (SRP)	Severe muscle involvement, rare but occasional lung involvement, no skin involvement
Anti-3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase	Severe muscle involvement, prior statin use (but 30% statin naïve), no skin or lung involvement

Antibody-negative immune-mediated necrotising myopathy	Increased risk of malignancy

- Acute presentation
- Severe muscle necrosis
- No extra muscular manifestations

Anti-synthetase syndrome 00:20:04

Anti-JO-1	Muscle involvement common, progressive interstitial lung disease, may have mild skin rash and mechanic's hands
Anti-PL-7	Severe interstitial lung disease, may have moderate muscle involvement
Anti-PL-12	Severe interstitial lung disease, may have mild or no muscle involvement
Anti-glycyl-transfer RNA synthetase (EJ), anti-OJ, anti-KS	High association with interstitial lung disease
Anti-Zo, anti-Ha	Rare, possible interstitial lung disease

- Anti-aminoacyl tRNA synthetase antibodies
  - Most common – anti Jo

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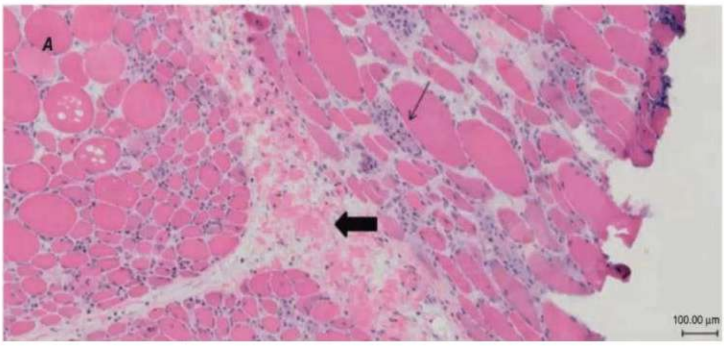

Fig: 10

Biopsy image

↓

Perifascicular atrophy

Overlap syndrome 00:22:02

- Myopathy associated with concurrent SLE, Sjogren's
- Associated with anti-Ro 52 antibodies
- EMG
  - More useful in dermatomyositis, IMNM
  - Fibrillation potentials
  - Positive sharp waves
  - Increase insertional activity
  - Low amplitude short duration
  - Polyphasic MUAP – Multiple Unit Action Potential

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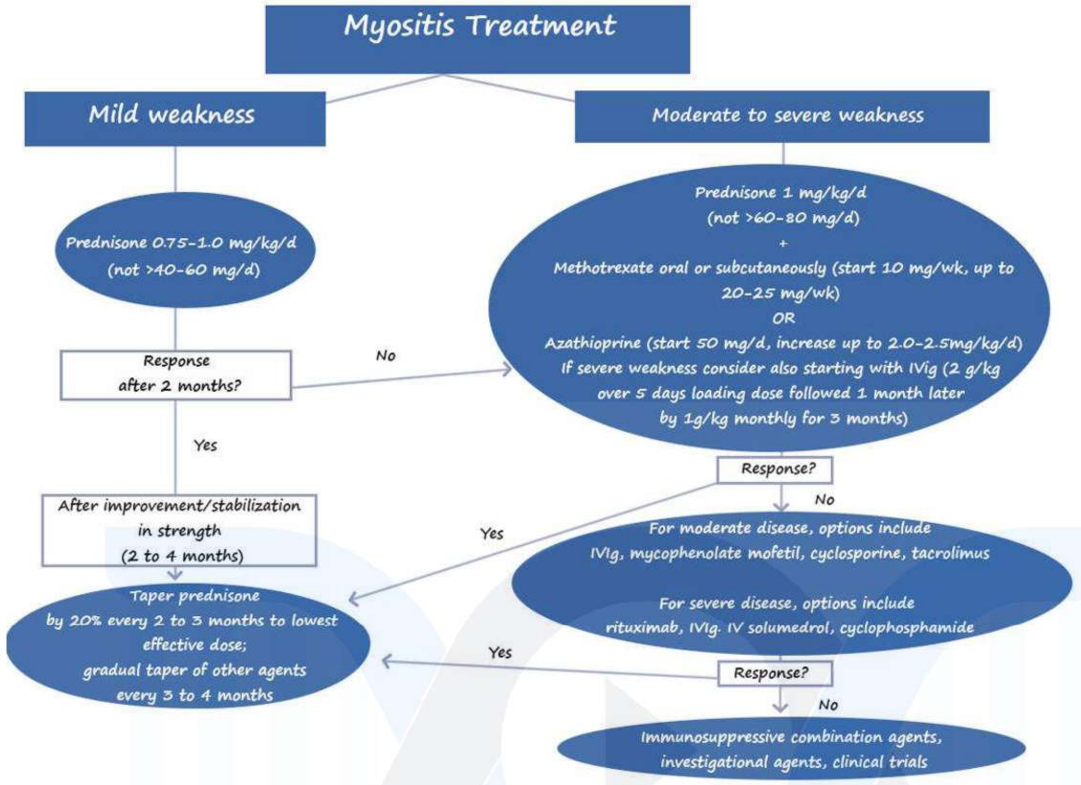
Treatment



Inclusion body myositis 00:28:45

- Most common in >50years of age
- Chronic progressive course
- Asymmetry ⊕
- Certain m/s groups selectively involved
  - Quadriceps
  - Finger flexors
  - Wrist flexors
  - Ankle dorsiflexors
- Sometimes facial weakness
- Associated with anti NTSC antibodies
- Biopsy:
  - Inflammation → atrophy

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- Sometimes ragged fibres ⊕
- Vacuoles (rimmed vacuoles)

Fig: 11

Treatment

- Poor response to immunosuppressants supportive therapy.

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INTRODUCTION AND BASICS OF HEMOLYTIC ANEMIA

- Anemia is characterized by premature RBC destruction or deceased RBC survival
- Life= 120 days
- Heterogenous group of disorder
- Diagnose by history → Physical examination, Peripheral smear, Lab values

Classification 00:02:52

1.Based on etiology

- Inherited
- Acquired

2. Based on clinical presentation

- Acute /subacute
- Chronic

3.Based on site

- Intrasaccular
- Extravascular (RE system)

4.Based on mechanism

- Intracapsular → mostly inherited
- Extra corpuscular → mostly acquired

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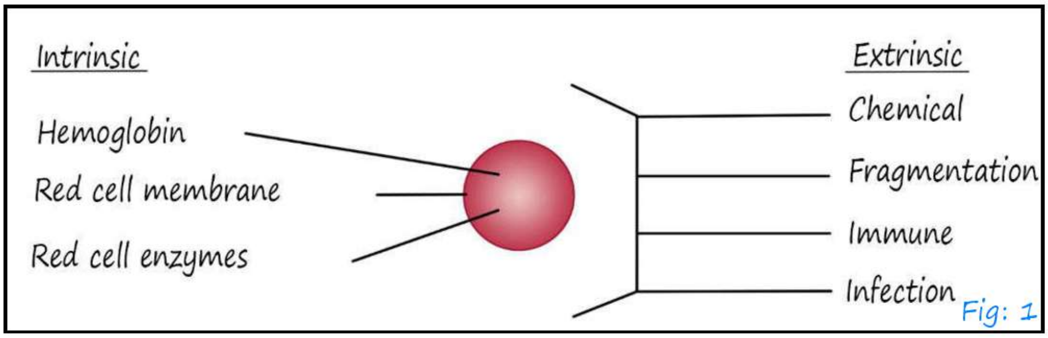

Fig: 1

Classification of Hemolytic Anemias		
	Intracorpuscular defects	Extracrpuscular factors
Inherited	Hemoglobinopathies enzymopathies membrane – Cytoskeletal defects	Familial atypical hemolytic uremic syndrome
Acquired	Paroxysmal nocturnal hemoglobinuria (PNH)	Mechanical destruction (Macroangiopathic) Toxic agents, Drugs, Infectious, Autoimmune

History 00:10:08

History

- Onset Duration
- Fatigue
- Jaundice
- Cholelithiasis
- Abdominal Pain
- Medication
- Infections

- H/O Cardiac/Valvular /Vascular Surgery
- High Colored Urine
- Family History – Jaundice
  Gall Bladder Disease
  Splenectomy
  Hereditary Anemia

Physical Examination 00:14:09

- Temperature
- Pulse Rate
- Pallor
- Icterus
- Splenomegaly

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Initial Laboratory tests for hemolysis		
Test	Finding in hemolysis	Cause
Haptoglobin	Decreased	Binds free hemoglobin
Lactate dehydrogenase	Elevated	Released from lysis of red blood cells
Peripheral blood smear	Abnormal red blood cells	Based on cause of anemia
Reticulocyte count	Increased	Marrow response to anemia
Unconjugated bilirubin	Increased	Increased hemoglobin breakdown
Urinalysis	Urobilinogen positive for blood	Free hemoglobin and its metabolites

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- Haptoglobin Decrease →Intravascular Hemolysis
- LDH Increase → Intravascular Hemolysis
- Peripheral Smear: - Fragmented Rbc's → Schistocytes
  →Macrocytes (Increase Mcv)
  →Polychromasia
  →Nucleated Rbc's
  →Reticulocyte Count
- Unconjugated Bilirubin Increased
- Urine Analysis: - Urobilinogen Increase (Extravascular Hemolysis)

  Hemoglobinuria, Hemosiderinuria] Intravascular Hemolysis
- Jaundice, Splenomegaly] Common with Extra Vascular Hemolysis

Features common to most patients with a hemolytic disorder	
General examination	Jaundice, pallor
Other physical findings	Spleen may be enlarged; bossing of skull in severe congenital cases
Hemoglobin level	From normal to severely reduced
MCV, MCH	Usually increased
Reticulocytes	Usually Increased

Bilirubin	Almost always increased (mostly unconjugated)
LDH	Increased (up to 10x normal with intravascular hemolysis)
Haptoglobin	Reduced to absent if hemolysis is at least in part intravascular)

History and physical examination findings	Suggested diagnosis
Diarrhea	Hemolytic uremic syndrome
Family history of hemolytic anemia	sickle cell disease, hereditary spherocytosis, thalassemias. G6PD deficiency
Fever	Autoimmune hemolytic anemia, disseminated intravascular coagulation, hemolytic uremic syndrome, infection
Hematuria	Paroxysmal nocturnal hemoglobinuria, intravascular hemolysis
Medications	Drug-induced thrombotic microangiopathic anemia, drug-induced immune hemolytic

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	anemia, G6PD deficiency
New-onset jaundice	Any hemolytic anemia
Personal history of cancer	Warm autoimmune hemolytic anemia
Personal history of mono nucleosis or Mycoplasma pneumoniae infection	Cold autoimmune hemolytic anemia
Recent transfusion history	Hemolytic transfusion reaction

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PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

- Disorder characterized by acquired chronic hemolytic anemia
- Classical triad: -
  - Persistent intravascular hemolysis with (exacerbation)
  - Pancytopenia (bone marrow failure)
  - Venous thrombosis
- Rare disease
- Males = Females
- Young adults (wide range)

Etiopathogenesis 00:05:09

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- Acquired intra corpuscular hemolytic anemia
- Acquired somatic mutation in 'PIG-A' gene
  ↓
  Located on x-chromosome

Deficient synthesis of a glycolipid moiety (Glycosyl – phosphor -inositol) [GPI]

- Deficient GPI linked protein
- GPI linked protein → important in regulating complement activity
  ↓
  1.CD 59 (membrane inhibitor of reactive lysis)
  2.CD 55 (decay accelerating factor)

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3.C8 binding protein

- CD59 – very potent inhibitor of c3 convertase
  - prevents spontaneous activation of alternate complement pathway
- CD 59 deficiency → RBC's susceptible to complement mediated intravascular hemolysis

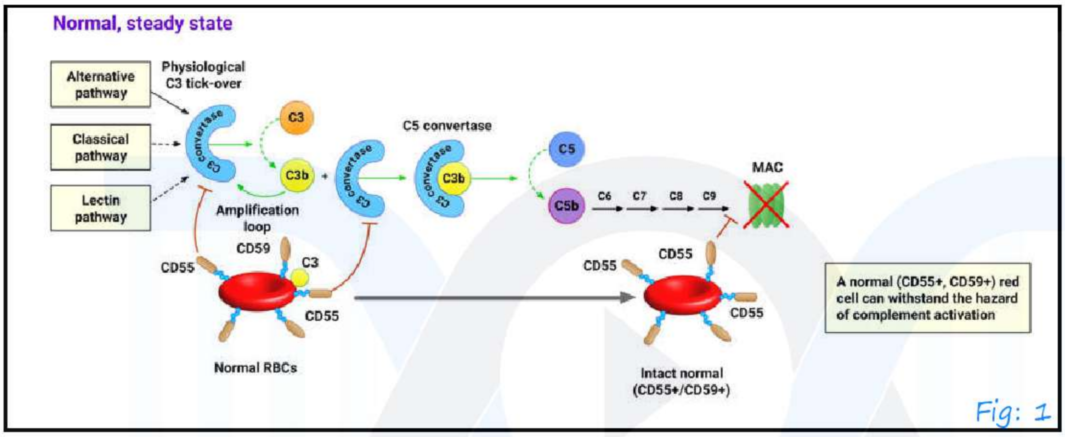

Fig: 1

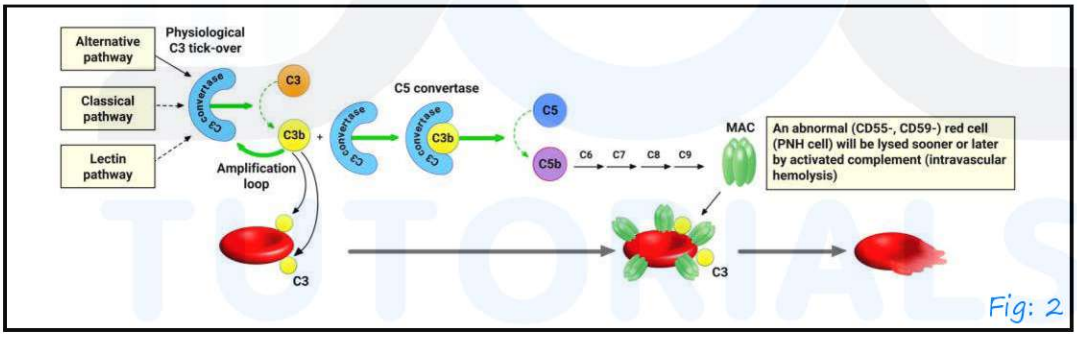

Fig: 2

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Clinical features 00:17:32

a. Intravascular hemolysis

- Intermittent hematuria

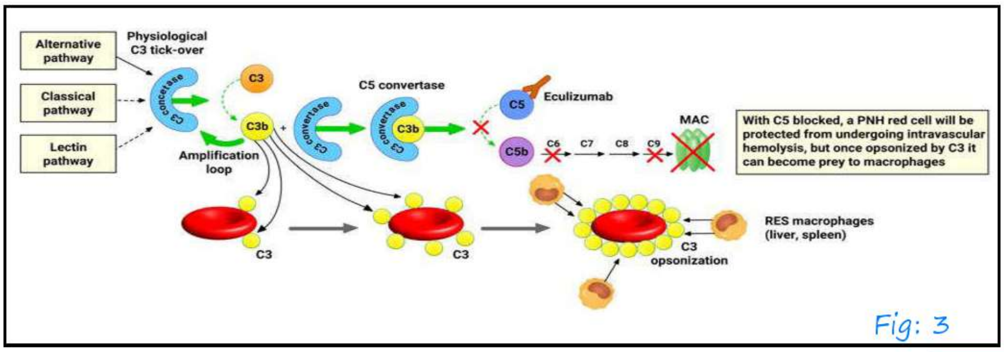

Fig: 3

- Anemia evaluation
- Night time: - decrease PH

  Increase RBC susceptibility to complement
- 25-30% only truly paroxysmal and nocturnal

b. Venous thrombosis

- Hepatic vein
- Mesenteric vein
- Portal vein
- Intracranial vein

(Hepatic, mesenteric, portal and intracranial veins:) Susceptible for venous thrombosis

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Why thrombosis?

1. Nitric oxide depletion

   Absorption of NO by free hemoglobin
2. Endothelial damage by MAC

   Acute onset of Budd – Chiari syndrome – abdominal pain and distension

c. Pancytopenia

- AML
- MOS

(AML, MOS:) <5 %

What brings patient to hospital

- Obvious hematuria
- Anemia
- Budd Chiari syndrome (cerebral venous thrombosis)
- Recurrent infection
- Bruising/easy bleeding
- Erectile dysfunction (because of NO depletion)

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Investigations:

- Anemia
- MCV high
- High reticulocyte
- High LDH
- low serum haptoglobin

Gold standard: flow cytometry

Other : acidified serum lysis test(hams test)

Sucrose lysis test

Bone marrow: erythroid hyperplasia

Treatment 00:31:16

i. Allogenic hematopoietic stem cell transplant (HSCT)

ii. Supportive treatment – transfusion

–Iron supplementation

iii. C5 complement inhibitors: – Eculizumab – Rovelizumab } Prevents Intravascular Hemolysis alone

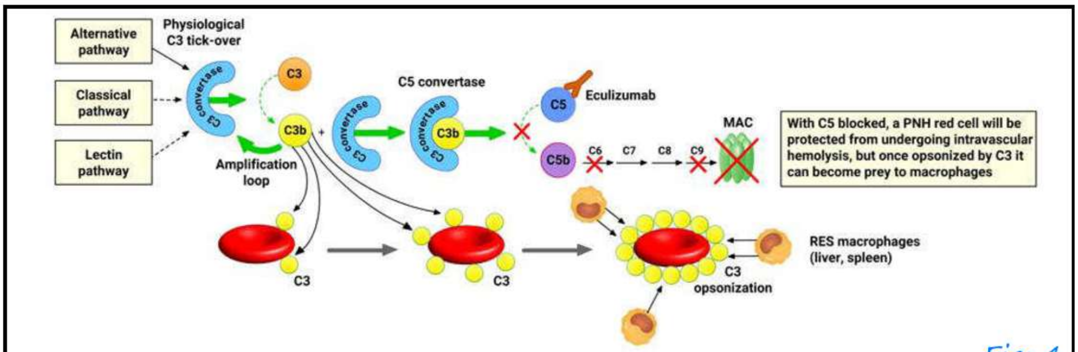

Fig: 4

iv. C3 complement inhibitor: - Pegcetacoplan

Prevents both intravascular and Extravascular hemolysis

- Eculizumab: - decrease venous thrombosis by 90%
- Symptomatic hemolytic PNH without bone marrow failure: -
  - C5 complement inhibitor
  - C3 complement inhibitor
- Subclinical PNH: -

  Watchful waiting
- PNA & AA: - Allogenic HSCT

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PLASMA CELL DISORDERS

- Group of disorders characterized by neoplastic proliferation of plasma cells
- Common cell of origin → post germinal center B cell
- Also referred to as – plasma cell dyscrasias
  - Monoclonal gammopathies
  - Para proteinemia's
  - Dysproteinemias

Disorders 00:03:25

- Multiple myeloma
- Walden storm's macroglobulinemia
- Primary amyloidosis
- Heavy chain diseases

  → 15% of death due to lymphoid neoplasms
- An antigenic exposure is required for conversion of B cells→ plasma cells
- There is clonal expansion of neoplastic plasma cells
- Monoclonal antibody response happens in plasma cell disorders

Why clinical manifestation? 00:08:01

- Mass of neoplastic plasma cells
- Products of neoplastic plasma cells

  ↓

  - Immunoglobulins
  - Subunits of Immunoglobulin
  - Lymphokines
- Host response to the tumor
- These plasma disorders form M component (monoclonal)

  ↓

  - Intact antibody molecule
  - Altered antibody
  - Fragments
  - Isolated heavy or Hight chains
- M component may have pathogenic consequences and act as tumor markers
- Complete M component will not appear urine. Light chains will appear → Bence Jones proteins
- < 30% of solitary plasmacytomas have M component
- 20% of myelomas will only have light chains

Detection of M component 00:14:45

- Serum protein electrophoresis → quantitative assessment
- Immune electrophoresis → qualitative assessment

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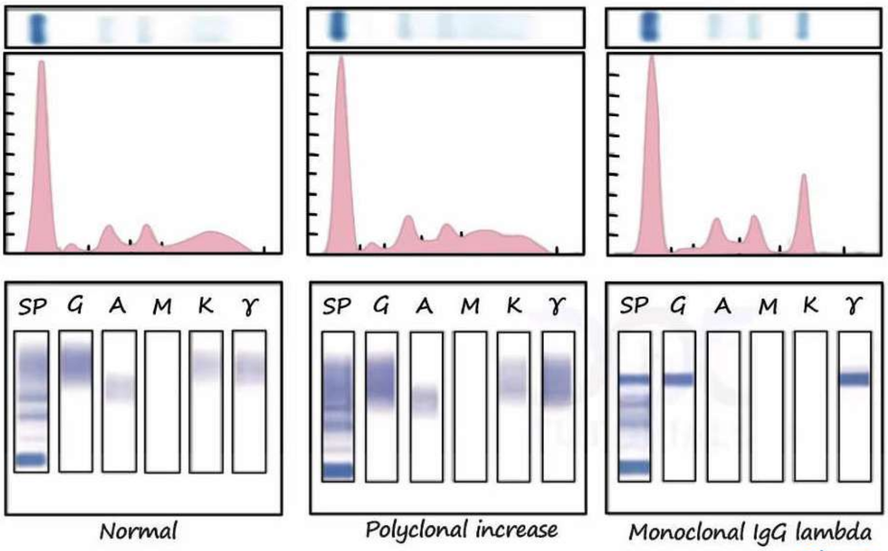

Fig: 1

M protein seen in

- CCL
- CML
- Breast cancer
- Colon cancer
- Gaucher's disease
- Cirrhosis
- Sarcoidosis
- Rheumatoid arthritis
- Myasthenia gravis.

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MULTIPLE MYELOMA-ETIOPATHOGENESIS & CLINICAL FEATURES

Multiple myeloma

- Defined as malignant proliferation of clonal plasma cells
- 10 % of all hematological malignancies is multiple myeloma

Etiopathogenesis 00:01:49

- No single exact cause
- Genetic factors
- Exposure to radiation, pesticides

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Genetic factors

- Mutated genes- K-RAS
  N-RAS
  BRAF
- Chromosomal rearrangement → IGH locus
  ↓ Chromosome 14 q
  Cyclin D1 gene
  Cyclin D3 gene
  MYC gene
- Deletion involving chromosome 17p
- IL-6 → prime driver for proliferation of survival of myeloma cells

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- Immunophenotype → positive for CD 138

  Syndrome -1

  CD 56

- Males > females
- Median age of onset – 69 years
- Multiple myeloma – asymptomatic pre-malignant phase

↓

MGUS (Monoclonal gammopathy of Undetermined significance)

- MGUS → multiple myeloma → 1% percentage /year
- > 50 years → 3% MGUS

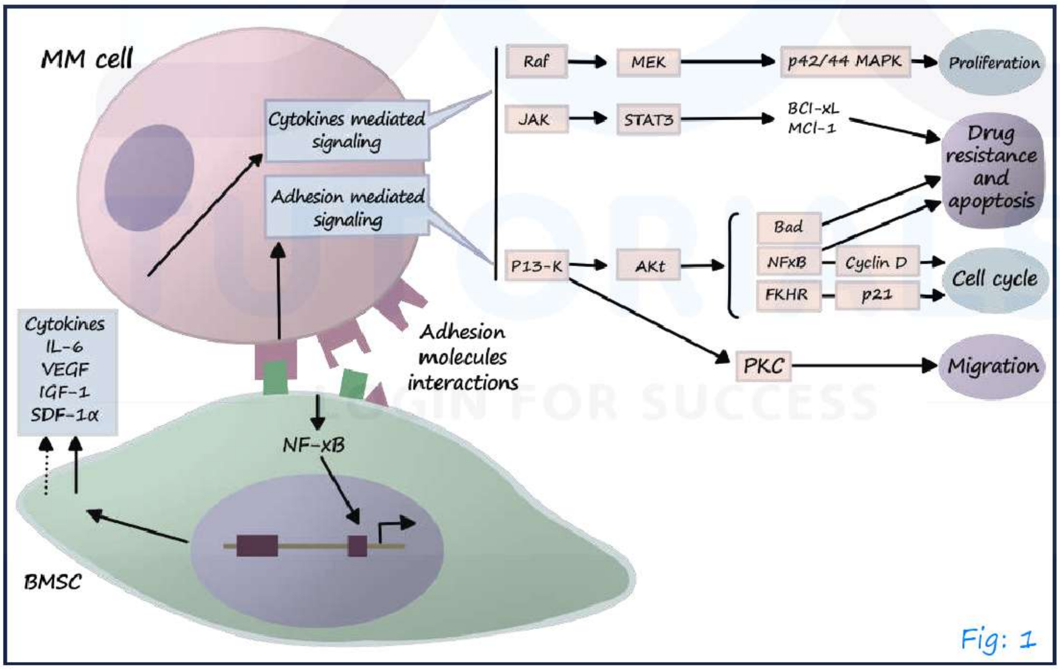

Fig: 1

- Interaction occurs between myeloma cell and bone marrow stromal cell via adhesion molecules
- End results – cell proliferation

  Increased survival

- MGUS → MM (multiple myeloma)

↓ ↓

Asymptomatic End organ damage

Clinical features 00:14:44

"CRAB "manifestations

- Hypercalcemia
- Renal dysfunction
- Anemia
- Bone lesion

i. Skeletal manifestation

- m/c symptoms -bone pain
- multiple myeloma produces OAF- osteoclast activating factor

↓

-Bone resorption

-Lytic bone lesion

(Punched out skull

Fig: 2

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- There is also osteoblast suppression -DKK-1
- Because of bone lysis – Acute 2 chronic manifestations of hypercalcemia

↓

- confusion
- weakness
- lethargy
- constipation
- polyuria

- Bone lysis can lead to pathological bone fracture

↓

- collapse of vertebra
- compressive myelopathy (or) radiculopathy

- affects – vertebral column
  - ribs
  - skull
  - pelvis
  - clavicle, femur, scapula
- Rarely, diffuse osteopenia can be present

ii. increases susceptibility to infections

why?

- hypogammaglobulinemia
- suppression of immune response→ antibody response

- dysfunction complement system
- granulocyte dysfunction
- Steroids
- Bortezomib → Increases risk of herpes infection
- What infections?
- Pneumonia
- Pyelonephritis

- May have recurrent infections
- Organism causing pneumonia→ pneumococcus
  Staph aureus
  Klebsiella
- Organism causing UTI: - E. coli and other gram-ve organism

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iii. Renal involvement in multiple myeloma

- 50 % will have renal pathology
- 25% will have renal failure
- Why? → pre renal
  → renal
  → post renal
- Hypercalcemia -mmc of renal failure in multiple myeloma
- Light chins appearing in urine are tubulotoxic
- Increased light chains → direct toxic effects
  Release of lysosomal enzymes
  - Renal injury caused by light chains

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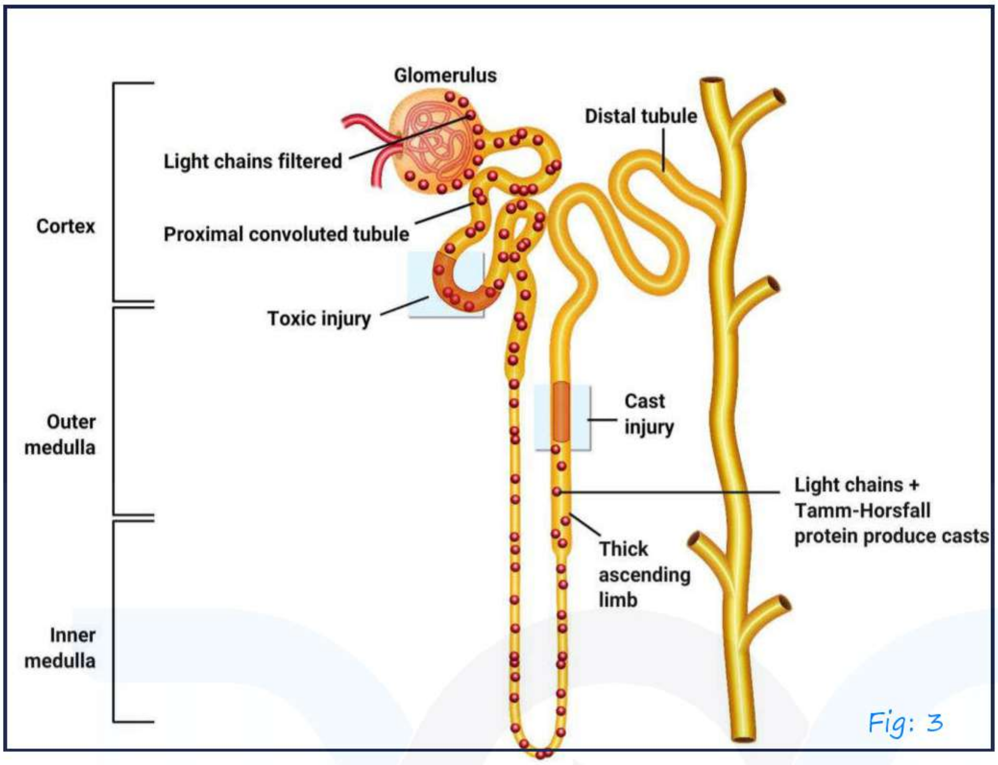

Fig: 3

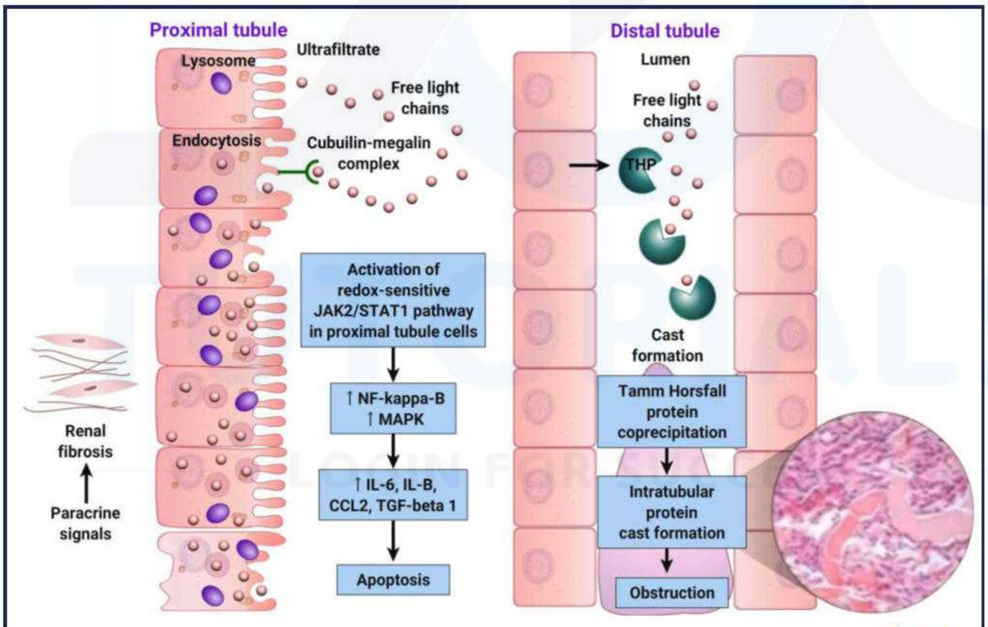

Fig: 4

What is the end results?

- Type 2 RTA (adult Fanconi's syndrome)

↓

Loss of glucose and amino acids

Inability to acidity and concentrate urine

- Proteinuria → BJP (Benz jones proteins)

- Other factor involved
  - Hyper -uricemia
  - Glomerular affection
  - Recurrent infections → AKI
  - NSAIDS → AKI

Renal pathology in patients with myeloma	
Histologic finding	Prevalence (%)
Myeloma kidney (myeloma cast nephropathy)	30-50
Interstitial nephritis / fibrosis without cast nephropathy	20 – 30
Amyloidosis	10
Light chain deposition disease	5
Acute tubular necrosis	10

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Etiology of renal injury and clinical manifestations in myeloma

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		Cause	Manifestation
Prerenal	Volume depletion Hemodynamic other	Hypercalcemia gastrointestinal losses (nausea and vomiting) sepsis hemodynamic from nsaids hyperviscosity (IgA, Igg3) hyperuricemia	Polyuria and polydipsia hypotension fever oliguria, hyperkalemia mental state alterations tumor lysis
Renal		Proximal tubular injury from light chains, uric acid, distal tubular injury from casts Glomerular disease (lcdd, amyloid)	Fanconi syndrome tubular proteinuria crystalluria nephrotic proteinuria hematuria, active sediment
Postrenal		Calculi	Colic

iv. Hematological abnormalities

- Normocyte normochromic anemia – 80%
  - Neoplastic plasma cell mass

    ↓

    Replaces normal bone marrow

→ Product of these cell cause inhibition of hematopoiesis

→ Decreased erythrocyte production

- Hemostatic disturbances
  - M component – interacts with clothing factors I, II, V, VII/VIII
  - Antibodies can coat platelets → platelet dysfunction
  - Endothelial damage
- Lenalidomide → Deep vein thrombosis

v. Neurologic abnormalities

- Hyper viscosity → headache
  Vertigo
  Ataxia
  Visual disturbances
- Hypercalcemia → lethargy
  Weakness
- Vertebral collapse → spinal card compression
  radiculopathy
- Carpal tunnel syndrome
- Peripheral neuropathy → MGUS, MM
  Sensory neuropathy > motor

IgM myeloma prone for neuropathy
Hyper viscosity

→ overall m.c subtype → Ig G

- Bortezomib, thalidomide → peripheral neuropathy

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MULTIPLE MYELOMA -WORK UP AND STAGING

Workup 00:01:23

- Anemia – Normocytic normotonic anemia
- Increase ESR
- A.G reversal
- ALP Normal
- S. creatinine , Blood urea
- S. Ca^{2+} increase
- β2 macroglobulin, albumin → involved in staging

Skeletal survey

- Plain x-ray → punched out lytic lesion (1-4cm)
- Peripheral smear: - Rouleaux formation

  - Normality, on the surface of RBC, There is zeta potential (negative charge)

  - in the multiple myeloma, zeta potential lost

↓

Stack of coins → Rouleaux formation

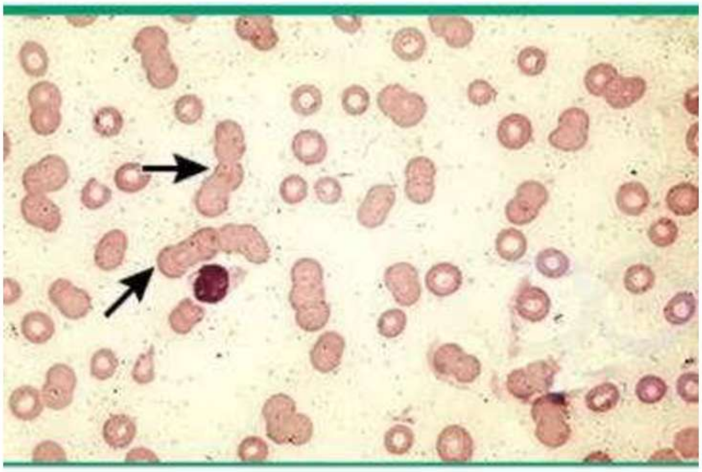

Fig: 1

- Leucopenia
- Thrombocytopenia
- Plasma cell leukemia

↓

When the absolute plasma cell count > 2000/ul (or) plasma cell count > 20% of peripheral WBC count

M protein detection

- SPEP or UPEP → 80% cases show localized band or peak

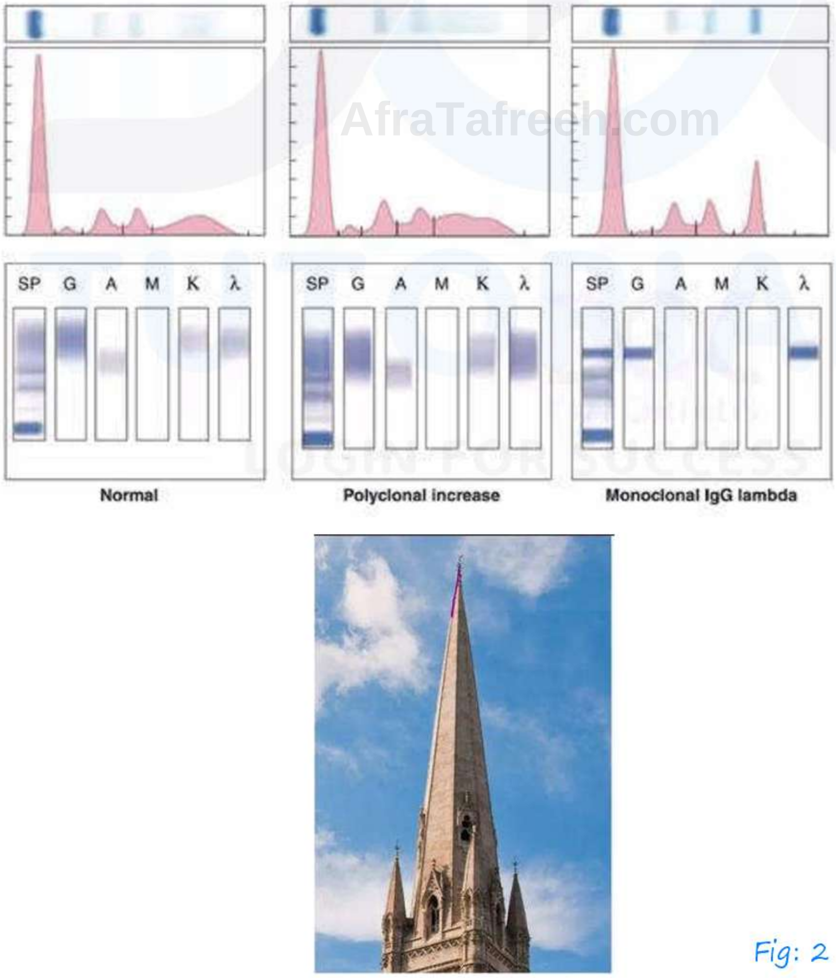

Fig: 2

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- Immunoelectrophoretic: - improves sensitivity to > 90%
- Serum free light chains analysis: - Normal kappa – lambda

FLC ratio

↓

0.26 – 1.65

- 90% cases will have abnormal free light chain ratio (FLC)
- M/c type: - IgG – 53% cased of MM

  IgA – 25 %
- 20% cases of multiple myeloma will have only light chains

Urine contamination

- Dipstick method: detects albumin only
- Sulfosalicylic acid test
- 24-hour urine electrophoresis and immunofixation
- Large waxy laminated casts

} to detect light chain

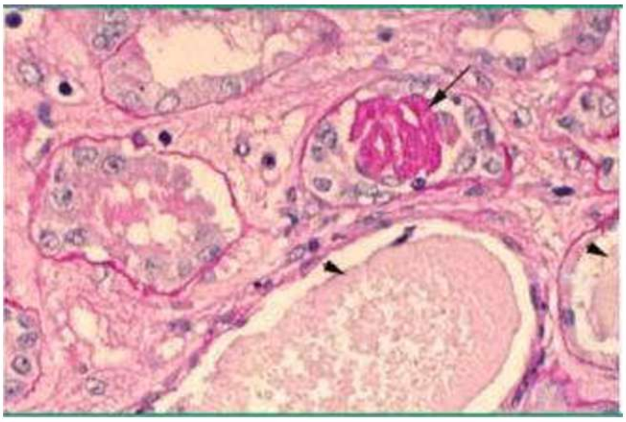

Fig: 3

Bone narrow examination

- Biopsy > aspirate

  ↓

  Plasma cell morphology and immunophenotype

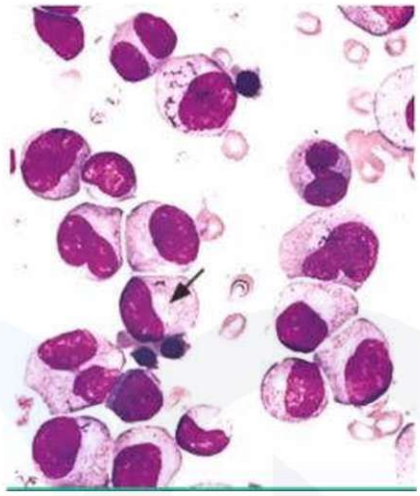

Fig: 4

Bone marrow aspirate

- Eccentrically placed nucleus,
- Perinuclear halo
- Prominent Golgi apparatus
- Mott cells → vesicle like inclusion

  ↓

  - Bunch of grapes
  - Immunoglobulin inclusion

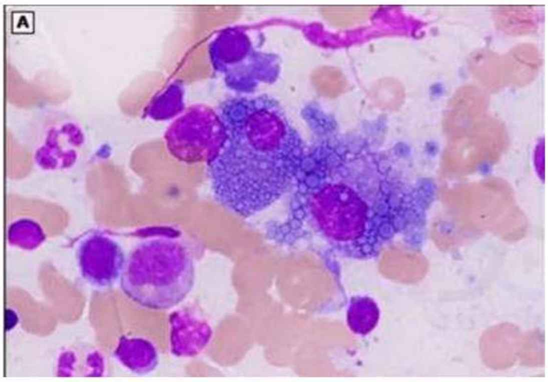

Fig: 5

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- If there are cytoplasmic inclusion – Russel bodies

  There is nuclear inclusion – Dutcher bodies

  → fiery red cytoplasm → Flame cells

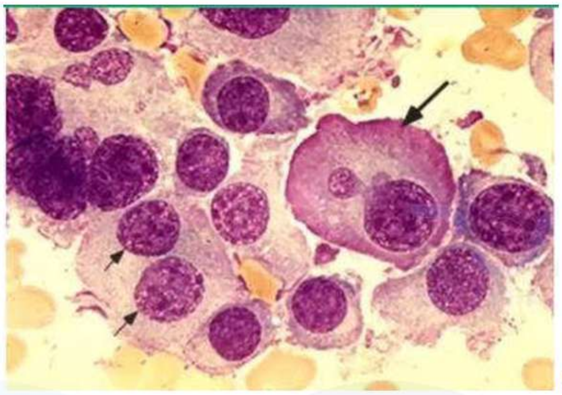

Fig: 6

Imaging 00:25:34

- MRI: – vertebral collapse

  Cord compression

  Extent of bone marrow infiltration

- FDG PET CT: – helps to find out bone lesions

  – to look for extramedullary involvement

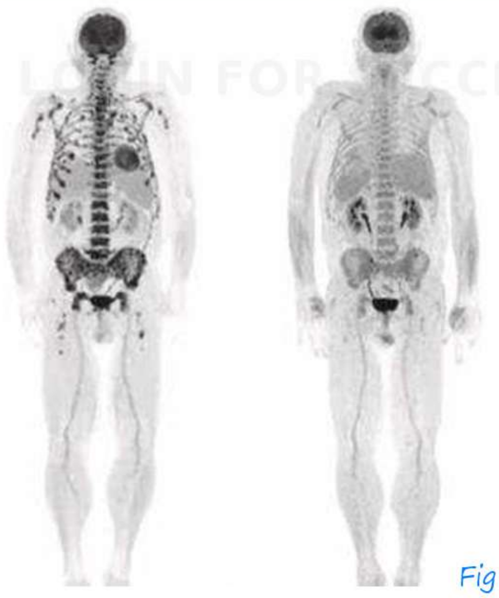

Fig: 7

Staging 00:27:00

- Durie -salmon staging

International Staging System		
	Stage	Median Survival, Months
β_2M <3.5, alb ≥ 3.5	I (28%)[a]	62
β_2M < 3.5, alb < 3.5 or β_2M = 3.5 – 5.5	II (39%)	44
β_2M > 5.5	III (33%)	29

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→ international staging system

↓

Parameters involved – β2 macroglobulin

– Albumin

- single most important determinant of staging

↓

β2 macroglobulin

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Risk Stratification in Myeloma		
CHROMOSOMAL ABNORMALITIES		
METHOD	STANDARD RISK (80%) (EXPECTED SURVIVAL 6-7+ YEARS)	HIGH RISK (20%) (EXPECTED SURVIVAL 2-3 YEARS)
Karyotype	No chromosomal aberration	Any abnormality on conventional karyotype
FISH	t(11:14) t(6:14) Del(13)	Del(17p) t(4:14) t(14:16) t(14:20) amp 1q34
INTERNATIONAL STAGING SYSTEM		
	STAGE	MEDIAN SURVIVAL, MONTHS
β_2 M<3.5, alb 23.5	I (28%)	62
β_2 M<3.5, alb <3.5 or β_2 M=3.5-5.5	II (30%)	44
β_2 M >5.5	III (33%)	29

- Other features suggesting high-risk disease:
- De novo plasma cell leukemia
- Extramedullary disease
- Elevated lactate dehydrogenates (LDH)
- High-risk gene expression profile

2015 – Revised ISS

↓

Includes chromosomal aberration LDH

T Revised International Staging System (R-ISS)		
R-ISS	Features	5-Y Overall Survival Rates (%)
R-ISS Stage I	ISS stage Ia No high-risk CA Normal LDH	82
R-ISS Stage II	Not R-ISS stage I or III[a]	62
R-ISS Stage III	ISS stage IIIa, and either of the following: High-risk CA or	40

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	Elevated LDH	

Standard Investigative Work up in MM
1. Investigations to Evaluate for Clonal Plasma Cells
Bone marrow aspirate and biopsy (fine needle aspiration of plasmacytoma if indicated) - Histology - Clonality by kappa/lambda immunostaining by flow cytometry or immunohistochemistry
2. Investigations to Evaluate Clonal Paraprotein
Serum protein electrophoresis and immunofixation Quantitative serum immunoglobulin levels (IgG, IgA, and IgM) 24-h Urine protein electrophoresis and immunofixation Serum free light chain and ratio Immunofixation for IgD or IgE in select cases
3. Investigation to Evaluate End-Organ Damage
Hemogram to assess for anemia Chemistry panel for renal function and calcium Skeletal survey to evaluate bone lesions

- PET/CT or MRI if SMM or solitary plasmacytoma with no other MDE or extramedullary disease
4. Investigation for Risk Stratification
-β-2 microglobulin and serum albumin for ISS stage - Fluorescent in situ hybridization for hyperdiploidy, del17p, t(4;14); t(14;16), amp1q34, and del 13 on bone marrow sample - LDH
Specialized Investigation in Selected Cases
Abdominal fat pad for amyloid Serum viscosity if IgM component or high IgA levels or serum M-component >7 g/dl

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Definition 00:40:32

- International myeloma working group (IMWG)

Definition of multiple myeloma
Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma-defining events:
Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:

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• Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL) • Renal insufficiency: creatinine clearance <40 mL per min or serum creatinine >177 µmol/L (>2 mg/dL) • Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L • Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CTA
Any one or more of the following biomarkers of malignancy: • Clonal bone marrow plasma cell percentage* ≥60% • Involved: uninvolved serum free light chain ratio ≥100 • >1 focal lesions on MRI studies §

Definition of smoldering multiple myeloma
Both criteria must be met:
• Serum monoclonal protein (IgG or IgA) ≥30g/L or urinary monoclonal protein ≥500mg per 24 hours and/or clonal bone marrow plasma cells 10 to 60% • Absence of myeloma defining events or amyloidosis
Definition of monoclonal gammopathy of undetermined significance
All three criteria must be met:
Serum monoclonal protein <30 g/L • Bone marrow plasma cells <10% • Absence of myeloma defining events or amyloidosis (or Waldenström macroglobulinemia in the case of IgM MGUS)

Nonsecretory Myeloma
No M protein in serum and/or urine with immunofixation Bone marrow clonal plasmacytosis ≥10% or plasmacytoma Myeloma-related organ or tissue impairment (end-organ damage, as described above)
Solltary Plasmacytom
Biopsy proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells Normal bone marrow with no evidence of clonal plasma cells! Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion] Absence of end organ damage such as hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) that can be attributed to a lymphoplasma cell proliferative disorder

- Bone plasmacytoma

Fig: 8

- Extramedullary plasmacytoma

Fig: 9

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- Extramedullary plasmacytoma – less likely to progress to MM – recurrence rare

Criteria for the diagnosis of POEMS syndrome
Mandatory major criteria (both required)
Polyneuropathy
Monoclonal plasma cell proliferative disorder (almost always lambda)
Other major criteria (one required)
Sclerotic bone lesions
Castleman disease
Elevated levels of vascular endothelial growth factor (VEGF)
Minor criteria (one required)
Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)
Extravascular volume overload (edema, pleural effusion, or ascites)
Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)
Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails)
Papilledema
Thrombocytosis/polycythemia

- P– Polyneuropathy
- O– Organomegaly
- E– Endocrinopathy
- M– Myeloma
- S – Skin changes

TREATMENT OF MULTIPLE MYELOMA

1.Diagnosis and risk stratification

2.Is the candidate for autologous stem cells transplant (ASCT) → key part of myeloma

Goals of therapy 00:02:33

- Systemic therapy
- Supportive measures

CLASS	AGENT
Immunomodulatory agents	Thalidomide (T)
	Lenalidomide (R)
	Pomalidomide (P)
Proteasome inhibitor	Bortezomib (V)
	Carfilzomib (K)
	Ixazomib (1)
Antibodies	Daratumumab (Da)
	Elotuzumab (E)
histone deacetylase	Panobinostat (Pa)
Alkylating agents	Melphalan (M)
	Cyclophosphamide (C)
	Bendamustine (B)
Steroid	Dexamethasone (D)
	Prednisone (P)

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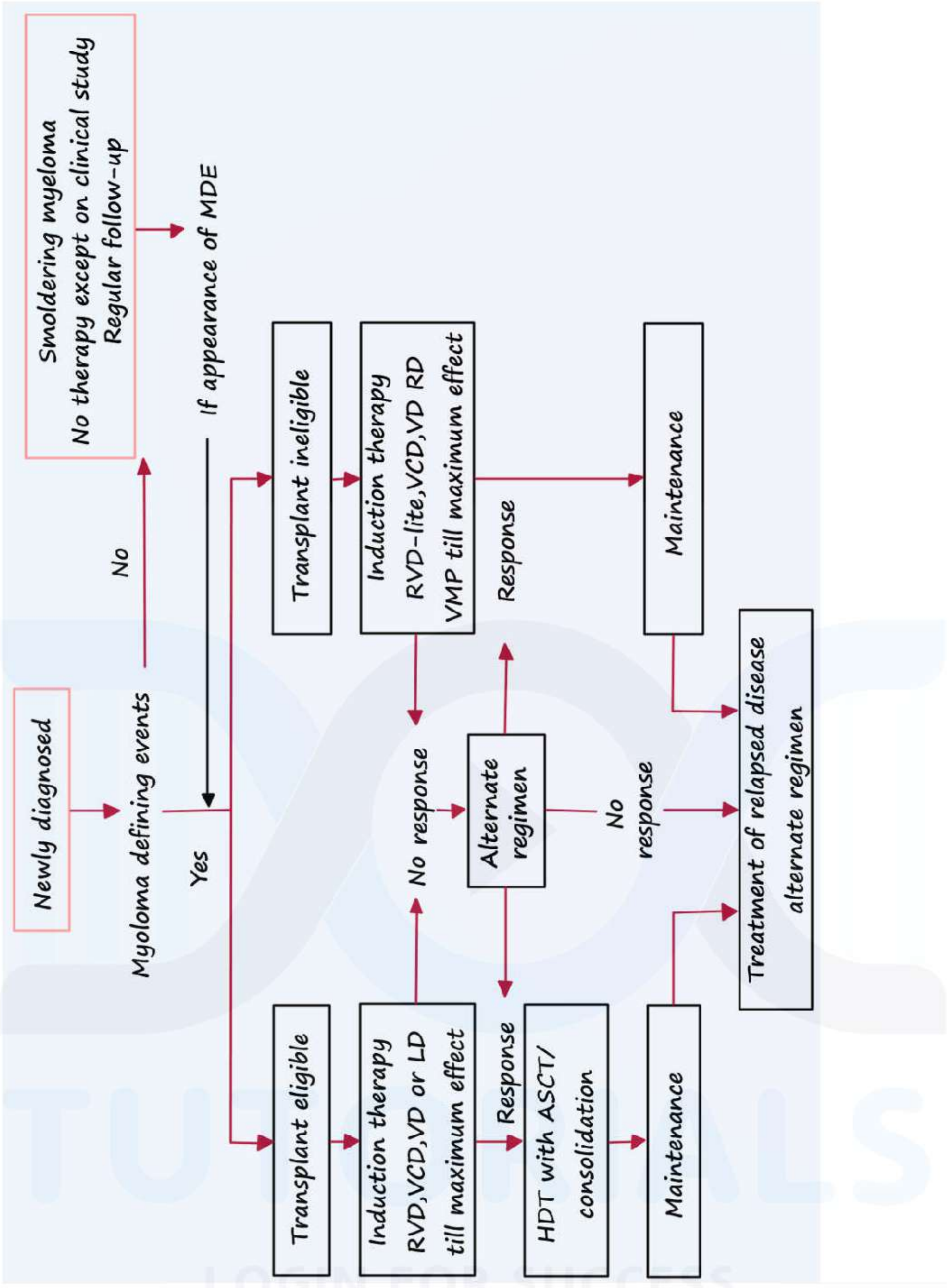


Mayo Guidelines

- Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomized, open-label, phase 3 trial
- Brian G M Durie, Antje Hovering. Muneer H Abide, S Vincent Rajkumar, Joshua Epstein, Stephen P Kahani,

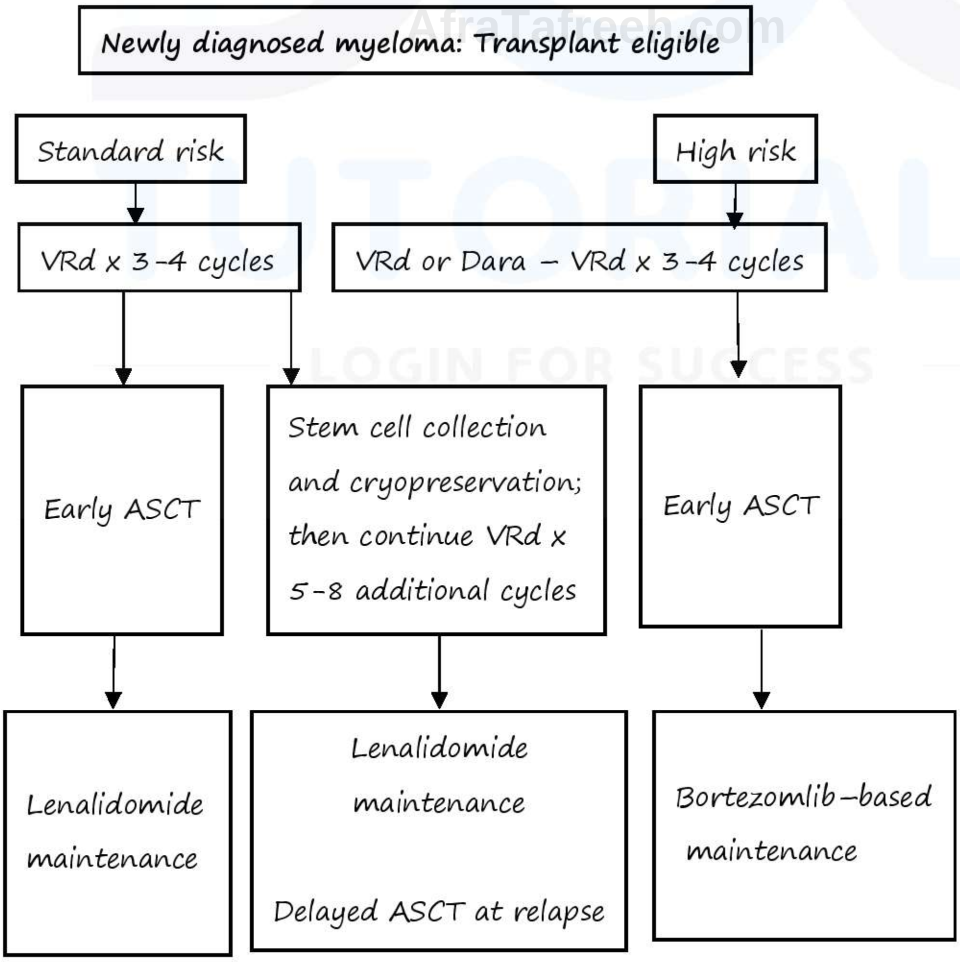
Mohan Thakur, Frederic Riau, Christopher M Reynolds, Rachael Sexton, Robert Z Orlowski, Bart Broglie, Angela Dispenser

- Combinations of triple drug therapy

↓

Protease inhibitor + immunotherapy + steroid

Bortezomib, lenalidomide, and dexamethasone
Carfilzomib, lenalidomide, and dexamethasone
Daratumumab, lenalidomide, and dexamethasone
Bortezomib, thalidomide, and dexamethasone
Bortezomib, cyclophosphamide, and dexamethasone
Ixazomib, lenalidomide, and dexamethason



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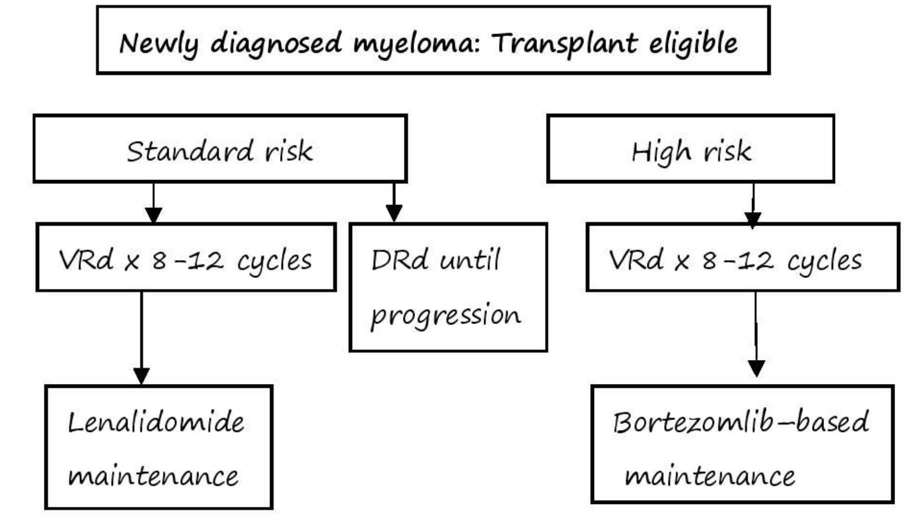
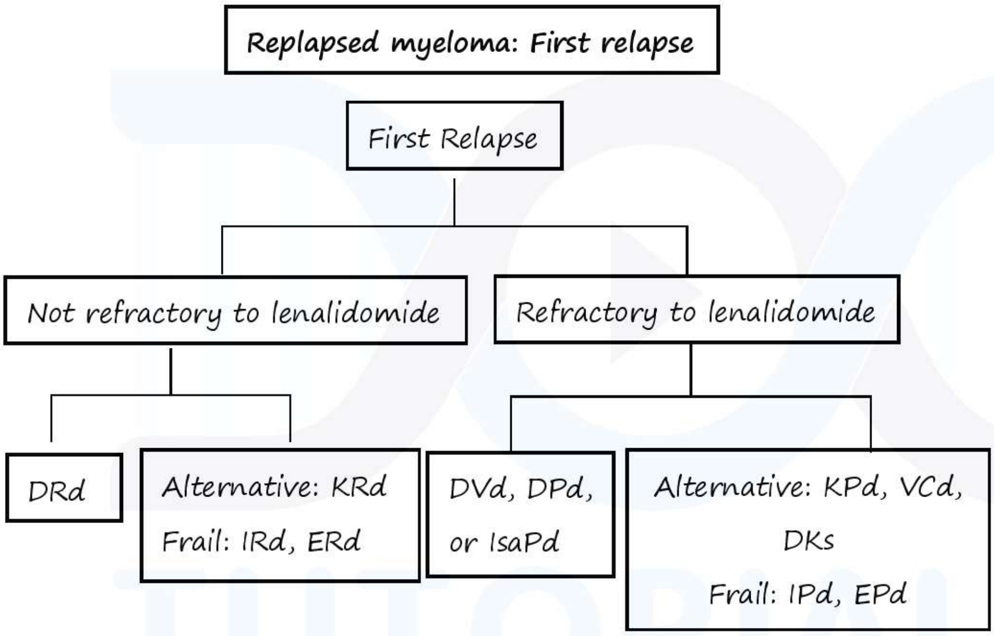




MGUS 00:21:36

- Wait and watch
- MGUS + Severe neuropathy

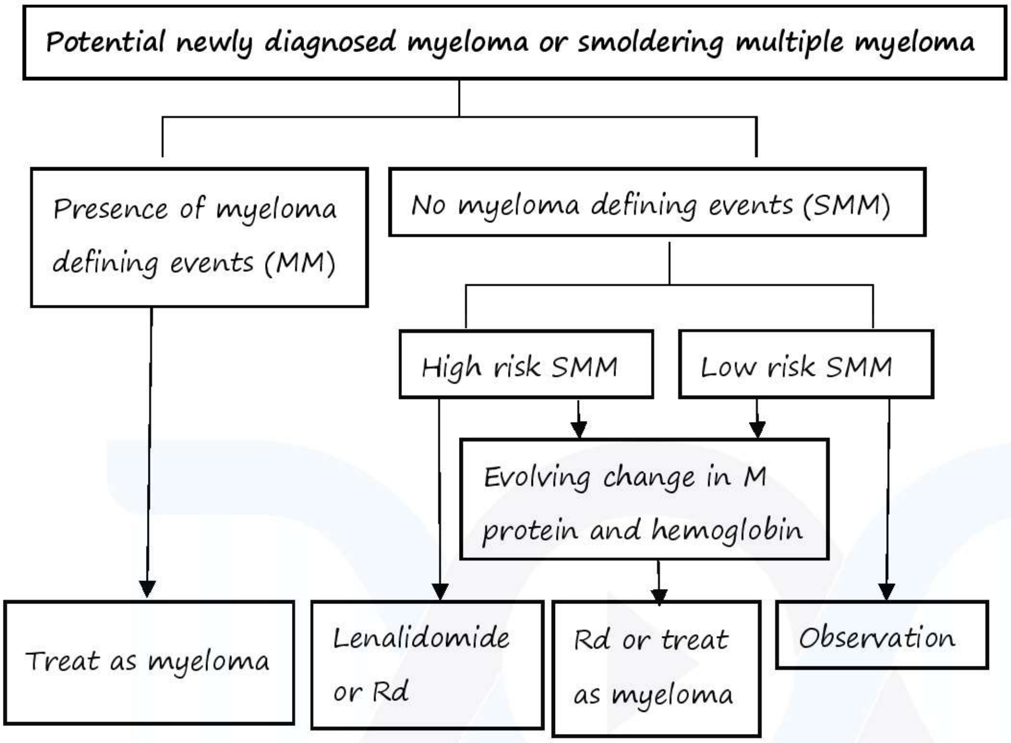
  IgG, IgA → similar to myeloma

  Ig D MGUS → Plasmaphereris and Rituximab

  Yearly follow-up required

Smoldering myeloma 00:23:24

- Wait and watch



High-risk SMM

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- Any 2-3 of the following high-risk factors:
  - Serum monoclonal protein >2 gm/dL
  - Serum free light-chain ratio (involved/uninvolved) >20
  - Bone marrow plasma cells >20%

Intermediate-risk SMM

- Any 1 high-risk factor

Low-risk SMM

- No high-risk factor
- Solitary plasmocytoma
  Extramedullary plasmocytoma

(Solitary plasmocytoma, Extramedullary plasmocytoma → Local radiation)

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Other management interventions 00:27:22

1. Hypercalcemia
   - Hydration
   - Steroids
   - Bisphosphonates
2. Neuropathy
3. Anemia

Preventive therapies 00:28:33

1. Skeletal lesions → Osteoclast inhibitor – bisphosphonates
2. Renal lesions → avoid NSAIDS
3. Infections → influenza, Pneumococcal vaccination
4. Thrombophylaxis.

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VON WILLEBRAND DISEASE

- Characterized by Quantitative /Qualitative defect in VWF
- Most common inherited blood disorder
- Prevalence: - 1 %

  Symptomatic VWD: -1 in 1000
- First discovered by Erick van Willebrand

  ↓

  Hereditary pseudo hemophilia

Etiopathogenesis 00:04:36

Von Willebrand factor

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- Large multimeric glycoprotein
- Encoded by a gene on chromosome 12
- Sources: - Endothelial cells & Megakaryocytes
- Stored in Weibel Palade bodies
- Seen in plasma - Sub-endothelial ECM

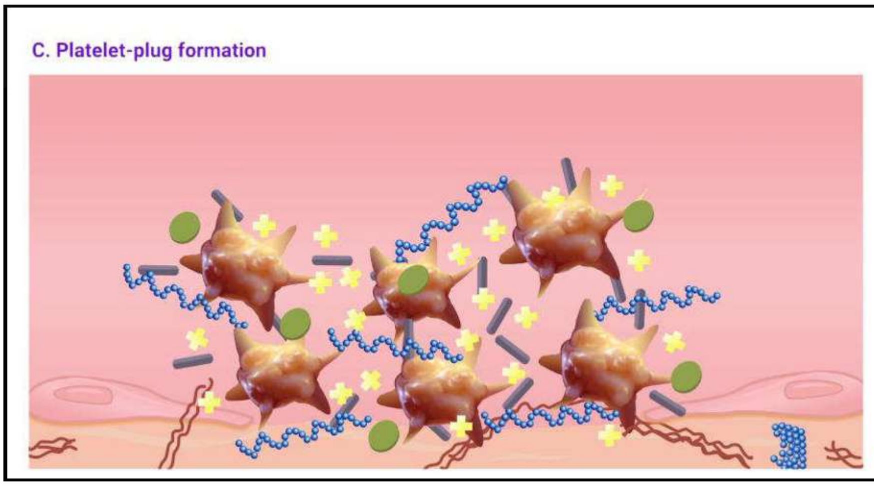

Fig: 1

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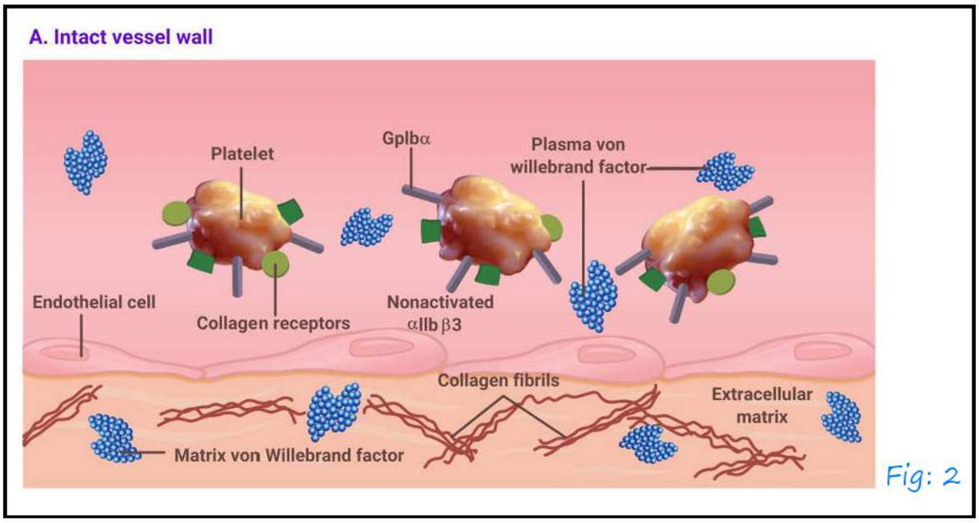

Fig: 2

- Normally VWF is in coiled state, in endothelial injuries, it is uncoiled state

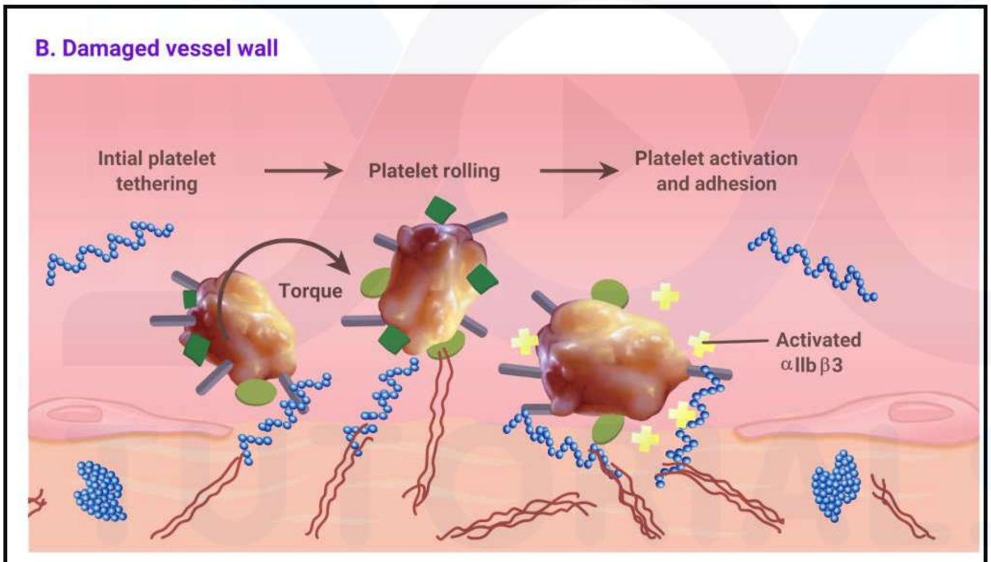

Fig: 3

Functions: – major adhesion molecule (large VWF multimers)

(Molecule glue)

Achieve hemostasis

– Binding protein for factor VIII

↓

Non -covalent complex with factor VIII

→ Prevent inactivation & clearance of factor VIII

↓

Prolong t1/2 of factor VIII

– Act as a plasma carrier and stabilizer of factor VIII

Types

- Type 1 2 3 – Quantitative defect VWF
- Type 2 – Qualitative defect

VWD type 1

- Most common (75-80%)
- Autosomal dominant
- Mild -moderate VWF deficiency (decrease VWF activity)
- Decrease VWF protein
- Decrease VWF function
- Decrease factor VIII levels
- Type 1c → increased clearance of VWF 15% of type I

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VWD Type 2

- Qualitative defect
- Autosomal dominant
- Subtypes

2A → most common among type 2
→ autosomal dominant
→ VWF is produced in normal amounts
→ Mis – sense mutation
↓
Defective multimer assembly
→ Large and intermediated multimers not present
↓
loss of platelet binding function of VWF

2B → AD
→ mutation resulting in abnormal structure of VWF
→ A, domain of VWF (binding site for GP1b)
→ Abnormally increase platelet binding by VWF

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- Gain of function defect
- Aggregates are removed by RES
- Thrombocytopenia

(2M) → mutation affecting A1 domain

↓

Decreased binding of platelet to VWD

(2N) → Autosomal recessive

→ Reduced binding of VWF to factor VIII

→ decrease Plasma factor VIII levels

→ phenotype similar to Hemophilic A

(Autosomal hemophilia)

Female with hemophilia like presentation

→ joint and soft tissue bleeding

Type 3: -

→ Autosomal recessive

→ Very low/indetectable levels of VWF

→ low levels of factors VIII (<10%)

Clinical features 00:37:27

- Vary among patients
- Manifests like platelets like disorder
  - Mucosal bleeding symptoms
  - Usually does not present in infancy
  - Later childhood
- Epistaxis
- Easy bruising
- Dental extraction
- Tonsillectomy
- Menorrhagia

(Dental extraction, Tonsillectomy, Menorrhagia) — increase bleeding

- Joint and soft tissue bleeds type 3 and type 2 N

Diagnosis 00:42:07

- History -mucosal bleeds
- Confirmation – lab tests

Lab investigation

- CBC
- Routine coagulation studies

} Rule out other disorders

Primary testing

- Bleeding time
- VWF antigen (ELISA)
- VWF activity (Ristocetin cofactor assay)
- Levels of factor VIII → <30 %

→ Bleeding time prolonged

Depends on blood group

Hormonal factors

Stress

Race

Environment

→ 'O' blood group individual has half of VWF of 'AB' blood group

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Primary testing

Ristocetin cofactor assay

- Adding ristocetin 1-2 mg/ml to a mixture
  - Patient plasma (source for VWF)
  - Washed normal platelets

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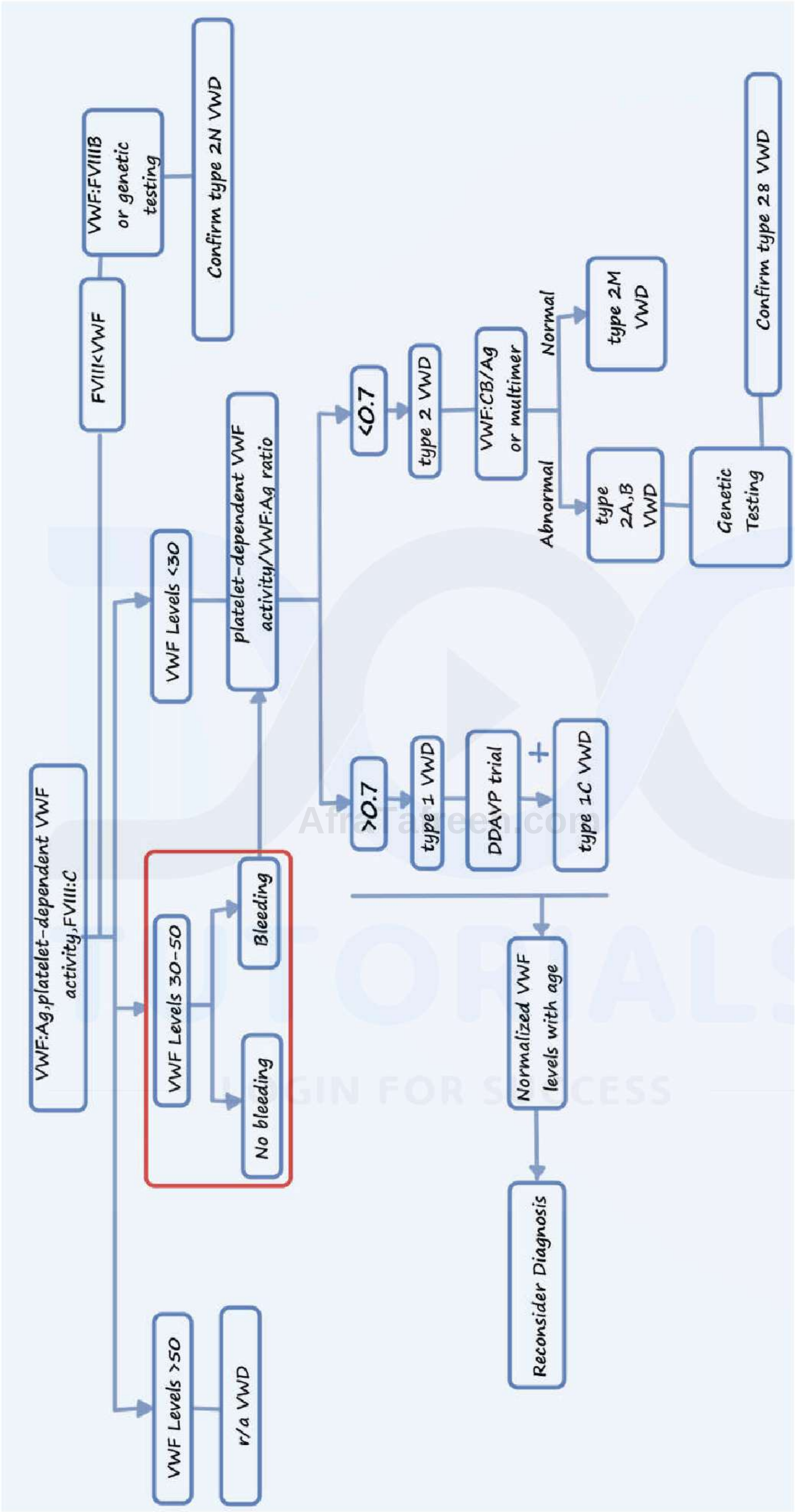
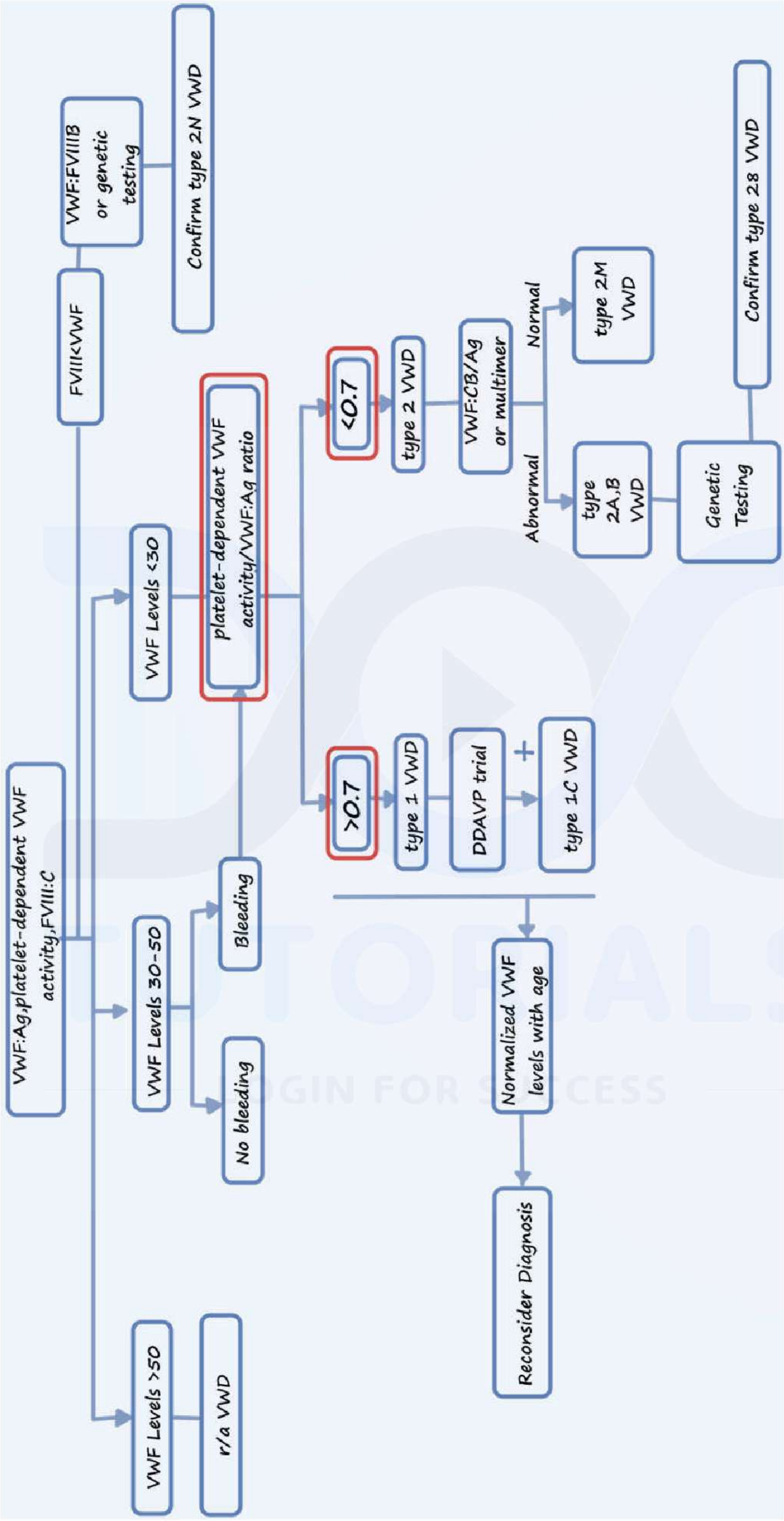
Secondary testing

- VWF multimer study
- Subtyping VWD type 2
- Therapeutic complication

Laboratory Diagnosis of von Willebrand Disease (VWD)					
TYPE	APTT	VWF ANTIGE	VWF ACTIVITY	FVIII ACTIVITY	MULTIMER
1	Nl or ↑	↓	↓	↓	Normal distribution, decreased in quantity
2A	Nl or ↑	↓	↓↓	↓	Loss of high- and intermediate -MW multimers
2B[0]	Nl or ↑	↓	↓↓	↓	Loss of high-MW multimers
2M	Nl or ↑	↓	↓↓	↓	Normal distribution, decreased in quantity
2N	↑↑	Nl or ↓[b]	Nl or ↓[b]	↓↓	Normal distribution
	↑↑	↓↓	↓↓	↓↓	Absent


VWF:Ag,platelet-dependent VWF activity,FVIII:C
FVIII<VWF
VWF:FVIIIB or genetic testing
Confirm type 2N VWD
VWF Levels <30
platelet-dependent VWF activity/VWF:Ag ratio
<0.7
type 2 VWD
VWF:CB/Ag or multimer
Abnormal
Normal
type 2A,B VWD
type 2M VWD
Genetic Testing
Confirm type 2B VWD
>0.7
type 1 VWD
DDAVP trial
+
type 1C VWD
VWF Levels 30-50
Bleeding
No bleeding
Normalized VWF levels with age
Reconsider Diagnosis
VWF Levels >50
r/a VWD


VWF:Ag,platelet-dependent VWF activity,FVIII:C
FVIII<VWF
VWF:FVIIIB or genetic testing
Confirm type 2N VWD
VWF Levels <30
VWF Levels 30-50
VWF Levels >50
r/a VWD
Bleeding
No bleeding
platelet-dependent VWF activity/VWF:Ag ratio
<0.7
>0.7
type 2 VWD
VWF:CB/Ag or multimer
Normal
Abnormal
type 2M VWD
type 2A,B VWD
Genetic Testing
Confirm type 2B VWD
type 1 VWD
DDAVP trial
+
type 1C VWD
Normalized VWF levels with age
Reconsider Diagnosis

Acquired VWD

- MGUS
- Multiple myeloma
- Walden Strom's macroglobulinemia
- Suspected in elderly patient with new onset severe Mucosal valvular disease
- Hyde's syndrome

↓

- Aortic stenosis + GI bleeding
- Angiodysplasia
- Increased degradation of VWF metalloproteinase (ADAMTB
- Not able to form multimers

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Treatment 00:03:33

Goal of treatment

- Increase VWF levels
  i. Desmopressin
  ii. Exogenous WF containing concentrates

Desmopressin: – V_2 receptors –vascular endothelium
- CAMP signaling
- secretion of VWF

↓

- useful in Type I VWD
- some cases of Type 2
- given intravenously /intranasal spray
- repeated infections – Tachyphylaxis
  - Hyponatremia

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VWF replacement products

- Useful in
  - Type 3
  - Some cases of Type 2 & 1

Type	Treatment	Comment
1	DDAVP: VWF replacement product	DDAVP effective in most patients
1C	DDAVP: VWF replacement product	Response to DDAVP often short-lived
2A	DDAVP: VWF replacement product	Response to DDAVP may not be as marked as in type 1
2B	VWF replacement product	DDAVP may worsen thrombocytopenia; perform therapeutic trial with measurement of post-DDAVP platelet count
2N	VWF replacement product	Low baseline FVIII levels typically require administration of FVIII replacement product in addition to VWF replacement product
2M	DDAVP; VWF replacement product DDAVP;	Response may not be as marked to DDAVP as in type 1
3	VWF replacement product	Very low baseline FVIII levels require administration of FVIII replacement product in addition to VWF replacement product

Antifibrinolytic agents

- EACA – used as an adjunct

Long term prophylaxis

- According to ASH 2021 → prophylaxis needed for severe and frequent bleeds

INTRODUCTION AND CLASSIFICATION OF MYELOPROLIFERATIVE NEOPLASM

- Group of disorders falling under category of myeloid neoplasms
- Characterized by myeloid proliferation independent of hematopoietic growth factors (HGF)

2016 WHO Classification of MPNS 00:03:19

- Chronic myeloid leukemia (bcr, abl)
- Chronic neutrophilic leukemia
- Chronic eosinophilic leukemia (Nos → not otherwise specified
- Polycythemia vera
- Essential thrombocytosis
- Primary myelofibrosis
- MPNS'S unclassifiable
- Masto cytosis
- All these disorders are characterized by increased production of one or more terminally differentiated myeloid elements

↓

Leads to increase peripheral blood counts

- HGF → bind to surface receptor of progenitor cells

↓

Activation of tyrosine kinase

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↓

Promotes growth & survival

- Growth factors independent proliferation
- Why? → acquired aberration in the signaling pathway
- These mutations do not impair differentiation
- Increased production of one or more mature blood elements

Summary of common features of MPN'S 00:12:17

- Origin: - Hematopoietic cells
- Overproduction without dysplasia
- Seeding of neoplastic cells to secondary lymphoid organs

↓

Extramedullary hematopoiesis

- Variable transformation to spent phase

↓

Characterized by marrow fibrosis and peripheral blood cytopenia's

- Transformation at varying rates to acute leukemia

Phenotypic heterogeneity

- CML
- CNL

] characterized by granulocyte hyperplasia

- CEL
- PV] characterized by erythroid or megakaryocyte hyperplasia
- PMF
- ET
- Genetic basis for the phenotypic heterogeneity

↓

- CML: - t (9,22)
- CNL: - t (15,19)
- CEL: - PDGFR α gene deletion/ translocation
- PV Directly or indirectly activate
- PMF] JAK2
- ET

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JAK2

- Tyrosine kinase
- Essential for function of erythropoietin and thrombopoietin receptors
- Utilized by G-CSF receptor
- These disorders (CML, CNL, CEL) are characterized by high rate of leukemic transformation
- PV] Transformation to acute leukemia is common
- PMF
- ET

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POLYCYTHEMIA VERA

- Clonal hematopoietic stem cell disorder characterized by trilineage myeloid involvement

↓

- Increased production of red cells, granulocytes and platelets
- Panmyelosis without a physiological stimulus

Etiopathogenesis 00:02:41

- > 95% cases → JAK – 2 tyrosine kinase mutation → chromosome 9p
- Replacement of valine with phenyl alanine at 617 residues of JAK – 2 → JAK 2 V617 F mutation

  ↓↓

  Constitutive tyrosine kinase activation
- In some cases, there might be frameshift or point mutation – exon 12 of JAK 2
- 30% of individuals may have chromosomal abnormalties

  ↓

  Deletion 20 q

  Deletion 13 q

  Trisomy 9
- Initial stages characterized by proliferative phase

  – Increase BM proliferative drive
- Spent phase: – characterized by

- Fibrotic transformation
- Extensive marrow fibrosis

↓

Displacement of hematoPoietic cells

- Extramedullary hematopoiesis in liver and spleen
- Massive hepatosplenomegaly

Clinical presentation 00:10:17

- Good majority
  - Incidentally
- Increase Hb
- Increase HCT
  - Hyperviscosity
  - Thrombosis
  - Hypermetabolism

  (Hyperviscosity, Thrombosis, Hypermetabolism → manifestations)
- Median age at diagnosis → 60 years
- Hyperviscosity symptoms
  - Headache, dizziness
  - Blurring of vision
  - Vertigo
  - Tinnitus
  - TIA
  - Systemic HTN
- Thrombosis symptoms
  - Venous and arterial thrombosis
  - Stroke
  - MI

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  - Budd chiari syndrome
  - Bowel injection
  - DVT
- Erythromelalgia
  - Burning pain
  - Reddish or bluish skin discoloration
  - Thrombocytosis and sticky platelets

  PV – most common cause of erythromelalgia
- Pruritis: - Aquagenic pruritis → Histamine release from basophils
- Vascular stasis: -
  - Digital ischemia and ulceration
  - Easy bruising
  - Epistaxis
  - Acid peptic disease
- Thrombocytosis → acquired VWD
- Hyperuricemia and uric acid stones
- 5 % individuals – symptomatic gout
- 2 % individuals – PCV - AML
- Examination
  - Plethoric and cyanotic appearance
  - 70 – 75% splenomegaly

Lab investigations 00:22:20

- Hb, HCT, Red cell count increased
- > 50% Neutrophilic leukocytosis

- 50% raised platelet count
- JAK – 2 mutations
- Trephine biopsy → hypercellular marrow with tri – lineage growth
- Serum erythropoietin decreased
- Serum uric acid increased

Diagnostic criteria 00:25:37

WHO PV criteria
Major criteria
1. Hemoglobin >16.5 g/dL in men
Hemoglobin >16.0 g/dL in women
or,
Hematocrit >49% in men
Hematocrit >48% in women
or,
increased red cell mass (RCM)*
2. BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
3. Presence of JAK2V617F or JAK2 exon 12
mutation
Minor criterion
Subnormal serum erythropoietin level

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Diagnosis: - 3 major (or) First 2 major + 1 minor

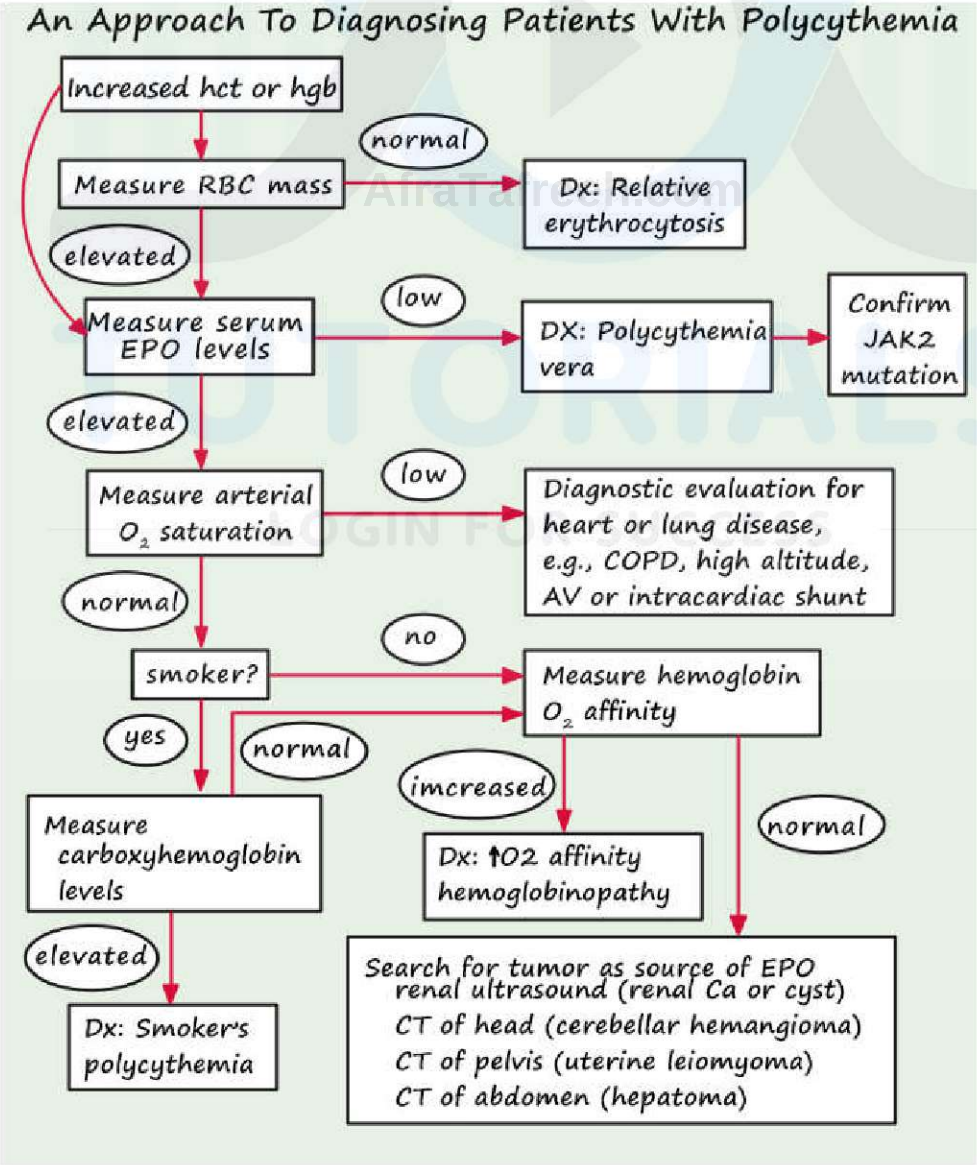
Causes of Erythrocytosis
Relative Erythrocytosis
Hemoconcentration secondary to dehydration, diuretics, ethanol abuse, androgens, or tobacco abuse
Absolute Erythrocytosis

Causes of Erythrocytosis	
Hypoxia	**Tumors**
Carbon monoxide intoxication	Hypernephroma
High-oxygen-affinity hemoglobins	Hepatoma
High altitude	Cerebellar hemangioblastoma
Pulmonary disease	Uterine myoma
Right-to-left cardiac or vascular shunts	Adrenal tumors
Sleep apnea syndrome	Meningioma
Hepatopulmonary syndrome	Pheochromocytoma
Renal Disease	**Drugs**
Renal artery stenosis	Androgens
Focal sclerosing or membranous	Recombinant erythropoietin
	Familial (with normal hemoglobin function)
	Erythropoietin receptor mutations

glomerulonephritis Postrenal transplantation Renal cysts Bartter's syndrome	VHL mutations (Chuvash polycythemia) 2,3-BPG mutation PHD2 and HIF2α mutations **Polycythemia vera**

Chuvash polycythemia

- AR
- AHL Mutation
- HIF 1 α ↑↑



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Gaisbock's complex

↓

- Symptom complex associated with polycythemia
- Not due to PV / hypoxia
- More common risk factors
  - Males
  - Smokers
  - Hypertensive
  - Diruretic
  - Obesity.

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TREATMENT OF POLCYTHEMIA VERA

Goals of Treatment 00:00:54

- Relieve clinical symptoms
- Decrease thrombotic risk
- Prevent bleeding events
- Minimizing risk of leukemic transformation

Risk Stratified Management

- Age
- H/O prior thrombosis
- Age < 60, no prior H/o thrombosis → low risk

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Low Risk Management 00:03:42

- Treatment of choice – phlebotomy

↓

- Reduces hype viscosity
- 500 ml removed → reduction in hematocrit by 3 % points
- Induce a state of iron deficiency

↓

Prevent accelerated re-expansion of red cell mass

- Target: - Hematocrit < 45 in men
  < 42 in women

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- Low dose aspirin

↓

Dealing with micro-vascular sequelae

→Extreme thrombocytosis > 1 million/mm^3

↓

Think of acquired VWD

↓

Measure Ristocetin co-factor activity (<30%) → Avoid aspirin

- Cytoreductive therapy
- Indicated in→ low risk – uncontrolled symptoms
  - Progressive increase in counts
  - Symptomatic or progressive splenomegaly
  - Poor tolerance to phlebotomy

High Risk Management 00:13:24

- Phlebotomy
- Low dose aspirin
- Cytoreductive therapy

Cytoreductive therapy

- Preferred 1st line: - Hydroxyurea

↓

  - Inhibitor of ribonucleotide reductase
  - 500mg BD (15 mg /kg/day)

- Does not prevent myelofibrosis
- Drug itself is leukemogenic
- Short duration

- Alternative: - pegylated INF-α → younger patient, pregnancy
  - Alkylating agent (Busulfan)
- II-line agents – Ruxolitinib
  - Anagrelide
  - Other alkylating agents
  - Radioactive phosphorus
- Ruxolitinib: - Nonspecific JAK-2 inhibitor
  - Constitutional symptoms decrease (severe pruritis)
  - Decrease spleen size
  - Reduces phlebotomy requirement
  - Refractory to hydroxyurea
- Anagrelide: - phosphodiesterase inhibitor
  - Lack marrow toxicity
  - Better in preventing thrombosis
- Pruritis: - Anti histamines, SSRI'S

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ESSENTIAL THROMBOCYTOSIS

- Clonal hematopoietic stem cell disorder
- Due to over production of platelets without a definite cause

Synonyms 00:01:47

- Hemorrhagic thrombocythemia
- Essential thrombocythemia
- Idiopathic thrombocytosis
- Primary thrombocytosis

Gene mutation 00:03:07

- 55% → JAK 2 V617F
- 36% → CALR (calreticulin)
- 4% → MPL gene- receptor for thrombopoietin

End result → Hyper- proliferation of progenitor cells

↓

Increase platelet count

Qualitative defects

Clinical features 00:05:34

- Elderly
- Females > males
- 50% cases – incidental detection'
- Vasomotor symptoms

- Thrombotic
- Hemorrhagic manifestation
- Vasomotor symptoms – Headaches
  - Visual disturbances
  - Erythromelalgia
  - Livedo reticularis
  - Acral paresthesia's
- Thrombotic symptoms – MI
  - Stroke
  - Budd Chiari
  - DVT

  } Very high platelet count
  Homozygous JAK2 mutation
- Hemorrhagic symptoms – Easy bruising
  Major hemorrhage
- Very low risk of leukemia transformation
- O/E – mild splenomegaly

Lab investigations 00:11:06

- Increase platelet count
- P. Smear: - Thrombocytosis
  Large platelets

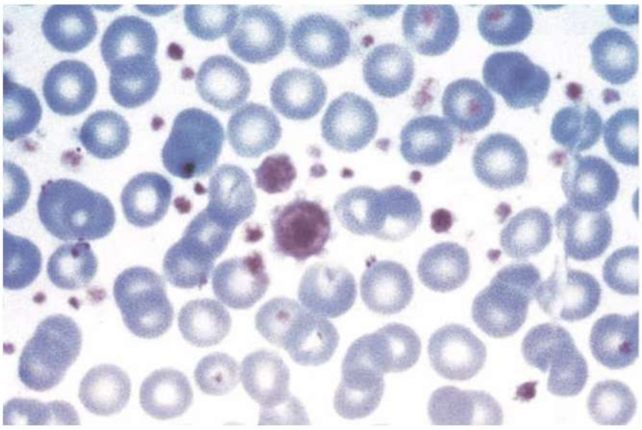

Fig: 1

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- Bone marrow: - Overall increase in marrow cellularity
  Megakaryocyte hypertrophy and hyperplasia

Treatment 00:13:28

- Majority – near normal life expectancy
- Asymptomatic, no cardiovascular risk factors, non-smoker
- Risk based management

Low risk
↓
- Age < O years
- No H/O thrombosis

↓
Low dose aspirin

High risk
↓
Low dose aspirin
+
Cytoreductive therapy

- Low risk + extreme thrombocytosis

↓

Low dose aspirin only if acquired von Willebrand disease is excluded

- Treatment Goal: - platelets < 4 lakh/mm3
  - Hydroxyurea – first choice
  - INF-α
  - Alkylating agents
  - Radioactive phosphorus

  (Alkylating agents and Radioactive phosphorus: Increase risk of leukemia)
- Plateletpheresis – acute settings

Causes of Thrombocytosis	
Tissue inflammation: collagen vascular disease, inflammatory bowel disease	Hemorrhage
Malignancy	Iron – deficiency anemia
Infection	Surgery
Myeloproliferative disorders: polycythemia vera, primary myelofibrosis, essential thrombocytosis, chronic myelogenous leukemia	Rebound: Correction of vitamin B_{12} or folate deficiency, post-ethanol abuse
Myelodysplastic disorders: 5q-syndrome, idiopathic refractory sideroblastic anemia	Hemolysis
Postsplenectomy or hyposplenism	Familial: Thrombopoietin overproduction, JAK2 or MPL mutations

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PRIMARY MYELOFIBROSIS

- Clonal hematopoietic stem cell disorder
- Characterized by – Marrow fibrosis
  - Extramedullary hematopoiesis
  - Splenomegaly
- Males > Females
- Common in 6th and 7th decade
- Lease common MPN
- Worst prognosis (Median survival – 5 years)
- Synonyms: – Idiopathic myelofibrosis
  - Angiogenic myeloid metaplasia
  - Myelofibrosis with myeloid metaplasia

Genetic mutation 00:04:10

- JAK2 V617F → 50% cases
- CALR → 20-25 %
- MPL → 8%

Pathogenic features 00:05:6

- Extensive collagen deposition by non- neoplastic fibroblasts
- Increase PDGF
- Increase TGF-B
- Osteosclerosis – Increase production of Osteoprotegrin (Osteoclast inhibitor)

Disorder causing myelofibrosis 00:07:27

Malignant	Non malignant
Acute leukemia (lymphocytic, myelogenous, megakaryocytic)	HIV infection
Chronic myeloid leukemia	Hyperparathyroidism
Hairy cell leukemia	Renal osteodystrophy
Hodgkin's disease	Systemic lupus erythematosus
Primary myelofibrosis	Tuberculosis
Lymphoma	Vitamin D deficiency
Multiple myeloma	Thorium dioxide exposure
Myelodysplasia	Gray platelet syndrome
Metastatic carcinoma	
Polycythemia vera	
Systemic mastocytosis	

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Clinical features 00:08:46

- 1/3rd of –asymptomatic at diagnosis
  - Abnormal blood counts
  - Splenomegaly
- Constitutional symptoms
  - Fatigue
  - Anorexia
  - Night sweats

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- Weight loss
- O/E – marked splenomegaly (splenic infarction)
  - Mild hepatomegaly

Lab investigation 00:11:53

- Anemic – Normocytic normochromic anemia
- Leukocytosis/leukopenia
- Thrombocytosis/thrombocytopenia
- Peripheral smear – features of extra medullary hematopoiesis
  - Tear drop RBC's
  - Nucleated RBC's
  - Leucoerythroblastic blood picture

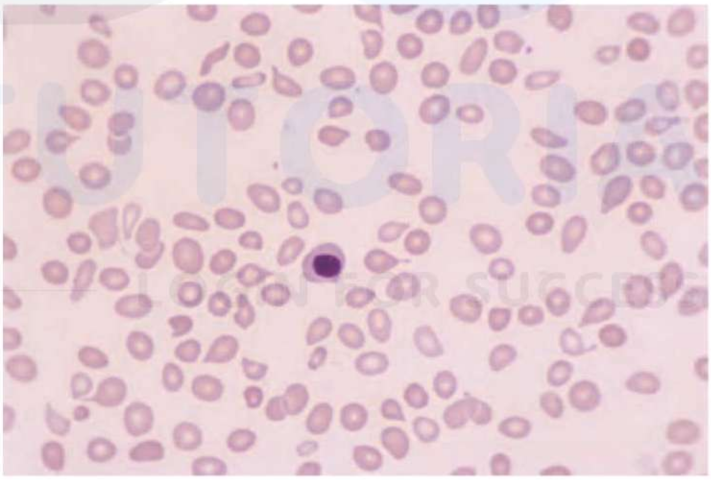

Fig: 1

Fig: 2

- Bone marrow findings – Fibrosis – mild to marked
  - Dry top /inaspirable marrow

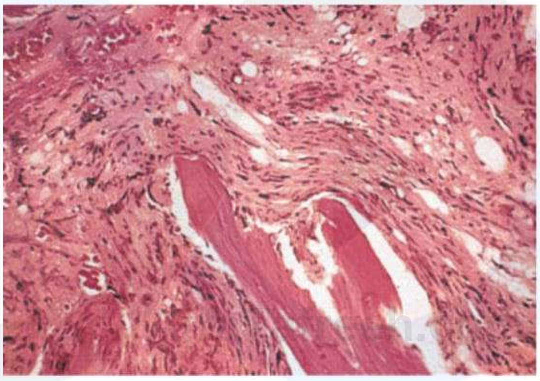
Fig: 3

- Bone x-ray: - Osteosclerosis
- LDH
- ALP
- Uric acid

Treatment 00:16:20

- No specific therapy
- Prognostication: - IPSS
- Blood transfusion
- Folic acid
- Ruxolitinib – can reduce splenic size

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- Decrease constitutional symptoms

- Steroids – mild benefit in anemia
  - Decrease constitutional symptoms
  - Improve thrombocytopenia

↑

Low dose thalidomide

- Curative Treatment: - Allogenic bone marrow transplantation

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CHRONIC MYELOID LEUKEMIA

- Chronic myelogenous leukemia
- Chronic granulocytic leukemia
- Clonal hemopoietic stem cell disorder
- Associated with chromosome 9,22 translocation
- acquired genetic disorder
- long arm of chromosome 9 is swapped with 22

  Gene on chromosome 9 – ABL 1 gene

  Gene on chromosome 22 – BCR gene

  ↓

  BCR ABL1 gene fusion → chimeric gene fusion
- Reciprocal balanced translocation

  ↓

  90% cases
- Chromosome 22 which has BCR ABL fusion gene is called Philadelphia chromosome
- Remaining 10% due to cytogenetically complex re-arrangements

  ↓

  FISH /PCR

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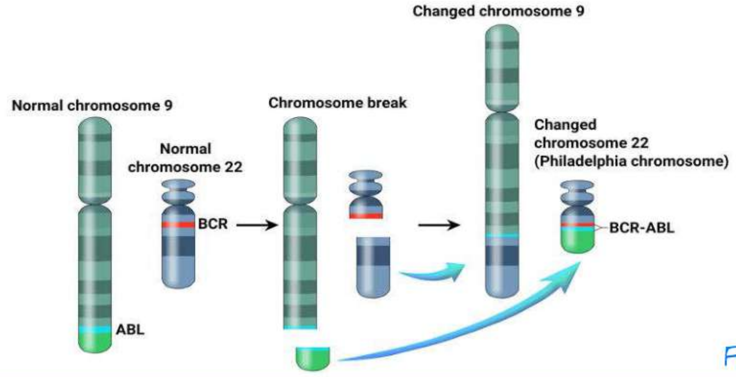

Fig: 1

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BCR ABL1 Fusion gene

↓

Oncoprotein

BCR- ABL1 – exhibit constitutive tyrosine kinase activity (Augmented granulocytes)

↓

Dysregulated production and uncontrolled proliferation of mature and maturing granulocytes

↓

Fairly normal differentiation

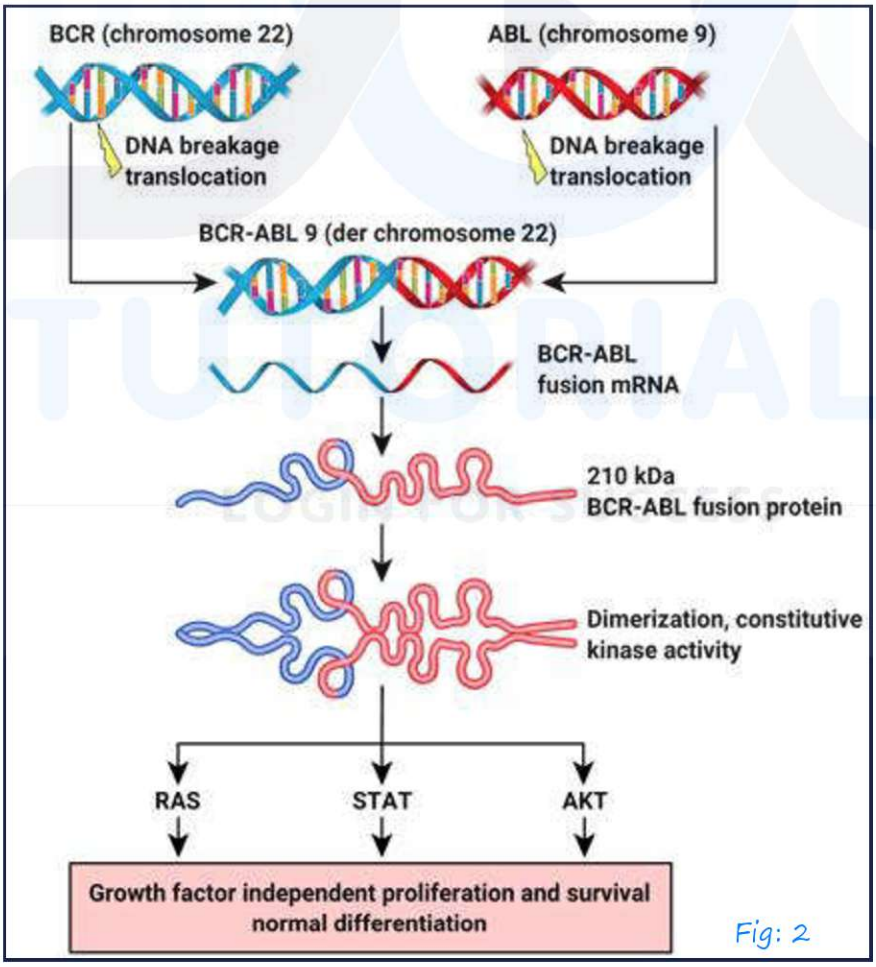

Fig: 2

- 15% of all cases of leukemia
- Slight male preponderance

- Median age at diagnosis: - 55-65 years
- No familial association
- Ionizing radiations – only known causative factor
- 6-8 years long period

Clinical cause 00:16:57

- Triphasic disease course – chronic phase
  - Accelerated phase
  - Blast crisis (blastic crisis blastic phase)

Chronic phase

- Myeloblast < 10% in blood or bone marrow

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Accelerated phase

- Myeloblast 10-19 %

  (or)

  Basophils ≥ 20%

  (or)

  Platelet < 1 lakh or > 10 lakh/mm3

  (or)

  Progressive increase in spleen size and increase WBC count not responding to treatment

  (or)

  Cytogenetic abnormalities in addition to Philadelphia chromosome

  ↓

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Trisomy 8

Isochromosome 17q

Duplication of Philadelphia chromosome

Blastic crisis

- Myeloblast > 20%
- 70% blastic crisis→ AML
- 30% Baltic crisis → ALL
- Can have myeloid blast crisis (or) lymphoid blast crisis
- Originates from pluripotent stem cells with myeloid & lymphoid potential

Clinical features 00:25:15

- 50-60 → asymptomatic at diagnosis

  Diagnosed at routine blood tests
- 90% present in chronic phase

Anemic symptoms

- Fatigue
- Malaise
- Weight loss

Splenomegaly

- Abdominal fullness
- Early satiety
- Left upper quadrant pain

Thrombotic tendency & hyper viscosity

- Arterial or venous thrombosis
- Visual disturbances
- Dyspnea & pulmonary dysfunction

Feature of bleeding diathesis

- Retinal hemorrhages
- GI bleeding

Accelerated & blastic phase

- Unexplained fever
- Significant weight loss
- Severe fatigue
- Bone and joint pain
- Infections
- Bleeding or thrombotic events
- Histamine release from basophils – pruritis
  - Flushing
  - Diarrhea
  - GI ulcers

Examination – m/c physical finding – splenomegaly

- 5-10% – Hepatomegaly
- Lymphadenopathy

- Skin or subcutaneous lesions – blastic crisis

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Investigations 00:34:43

- Blood counts – leukocytosis > 1 lakh
  - Platelet N /elevated
  - Normocytic normochromic anemia
- Thrombocytopenia – worse prognosis
  - Disease acceleration
  - Unrelated etiology
- P. smear – shift to left hematopoiesis
  - Neutrophils
  - Band forms
  - Metamyelocytes
  - Myelocytes
  - Eosinophils
  - Basophils –
- Basophilia – hall mark of CML
  - >1000/mm3
- Blasts <10%
- Bone marrow findings:
  - Hypercellular marrow
  - Marked myeloid metaplasia
  - Massively increased number of maturing granulocytic precursor
  - Megakaryocytes increase (small & dysplastic)
  - Erythroid progenitors ↓

N or mildly decreased

- Scattered macrophages

↓

Green blue cytoplasm

Sea blue histocytes

- Increase reticulin deposition

↓

Significant bone marrow fibrosis is rare

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Biochemical abnormalities

- Low LAP score
- PV
- Leukemoid reaction
- Increased uric acid
- Increased LDH

(PV, Leukemoid reaction, Increased uric acid } increase score)

Confirmation of diagnosis 00:44:42

- Bone marrow cytogenetics (conventional karyotyping) Philadelphia chromosome
- Detection of BCR- ABl1 fusion gene is the blood
  - FISH
  - PCR
- > 95% CML – demonstrate Philadelphia chromosome
- Philadelphia chromosome present in 20% ALL
  2% AML

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FISH

- More sensitive than cytogenetics
- Can be done in blood
- Cells are treated with probes having fluorescent dyes examined in microscope
- Detecting and count cells with BCR-ABL1 gene

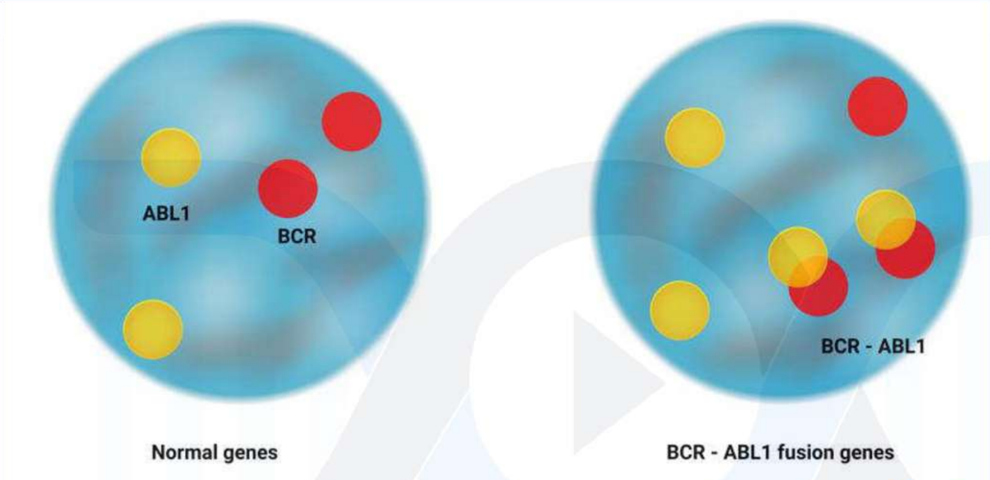

Fig: 3

RT Q PCR

- Quantitative reverse transcriptase PCR gene
- Most sensitive test to detect BCR – ABL1 fusion gene
- Quantifies BCR-ABL1 mRNA transcripts
- Diagnosis and monitoring after treatment

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TREATMENT OF CML

Management of CML 00:00:30

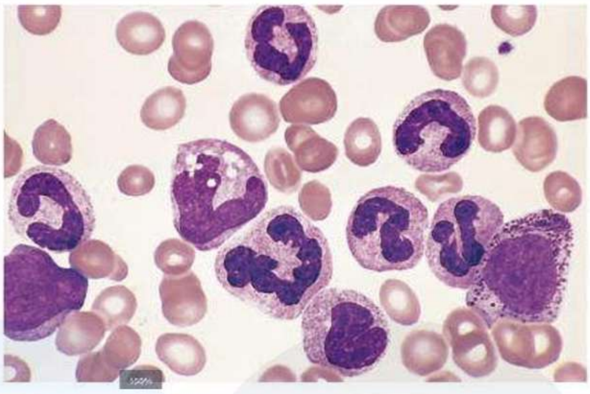

Fig: 1

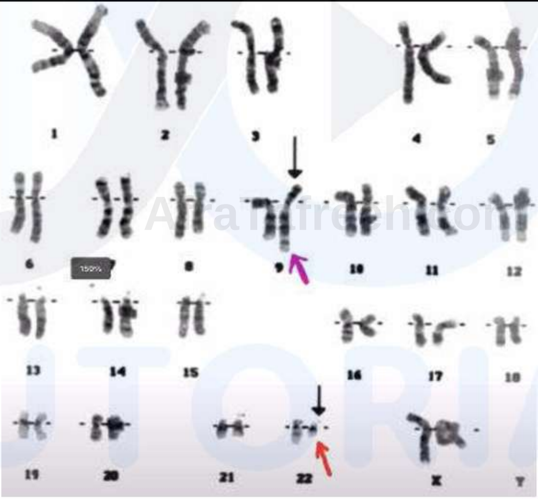

Fig: 2

- 6 FDA approved agents: -
  - 5 oral tyrosine kinase inhibitors
  - 1 protein synthesis inhibitors – omacetaxine

Tyrosine kinase inhibitors 00:04:06

- Act by targeting constitutively active tyrosine kinase
- 2001 – FDA → Imatinib → 1st generation TKI
- Previously 10-year survival < 30%

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- Currently 10-year survival 85%
- 2nd generation TKI: -
  - Dasatinib
  - Nilotinib
  - Bosutinib

- 3rd generation TKI: - ponatinib → effective for BCR – ABL,

  Mutation subtype T315 1
  ↓
  Resistant to other TKI

- How to measure response to TKI?
  - Hematologic response
  - Cytogenetic response
  - Molecular response

Hematologic response

- CBC and physical examination
  WBC < 10,000/mm³ with no immature granulocytes
  < 5% basophils
  Platelet count < 4.5 lakhs
  Spleen not palpable

Cytogenetic study

- Conventional karyotype
- Calculate % of Philadelphia positive chromosome cells

Fish test

- Calculate % of BCR – ABL, fusion gene

Complete cytogenetic response

- Cytogenetic study – no Philadelphia positive cells

  (or)

  Fish < 1% BCR – ABL 1 fusion gene

Major cytogenetic response

- < 35% of cells in BM have PH chromosome

Molecular response

- GPCR – detects BCR – ABL_1 transcript

  Major molecular response (MMR) → ≤ 0.1%

  Deep molecular response (DMR) → ≤0.0032%
- Imatinib – 400mg / day

  ↓ not responding

  - Increase dose – 600 mg / day
  - Switch to another TKI
  - Metabolized by $CYP_3 A_4$
  - Avoid cytochrome inducers and inhibitors
  - Monitoring – blood counts and differential counts

    ↓

    Every 2 weeks

  - until complete hematological response is achieved
- Q PCR
  - Must be performed at least every 3 months

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- Even after MMR is achieved

↓

To decide an eligibility for treatment discontinuation

Role of cytogenetics?

- Atypical translocation
- Rare or atypical BCR – ABL 1 transcripts
- Treatment failure / resistance
- Progression to AP or BP

↑↑↑ WBC counts

- Hydroxyurea
- Allopurinol: - 300 mg daily to minimize chance of tumor lysis syndrome

CML – Resistant to imatinib

- Insufficient drug level
  - Drug compliance
  - $Cyp3A_4$ inducers
  - Increase dose 600mg or 800 mg
- T315 I mutation – Ponatinib
- Additional chromosomal abnormalities
- Around 6% of CP → AP or BP
- Around 10% of CML → present with AP or BP
- AP or BP → 2nd generation TKI

  Imatinib 600 mg

Treatment free remission

- Eligibility for stopping TKI
  - Adults in chronic phase on TKI ≥ 3 years
  - Who has achieved DMR ≥ 2 years?
  - Who are willing to have close monitoring with Q PCR?

Allogenic Stem Cell Transplant

- TKI Failure
- Blastic phase – TKI + chemotherapy

↓ → Allogenic stem cell transplant

as soon as Remission possible

Leukemia (2020) 34:966–984
https://doi.org/10.1038/s41375-020-0776-2

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REVIEW ARTICLE

Chronic myelogenous leukemia

European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia

A. Hochhaus[1] · M. Baccarani[2] · R. T. Silver[3] · C. Schiffer[4] · J. F. Apperley[5] · F. Cervantes[6] · R. E. Clark[7] · J. E. Cortes[8] · M. W. Deininger[9] · F. Guilhot[10] · H. Hjorth-Hansen[11] · T. P. Hughes[12] · J. J. W. M. Janssen[13] · H. M. Kantarjian[14] · D. W. Kim[15] · R. A. Larson[16] · J. H. Lipton[17] · F. X. Mahon[18] · J. Mayer[19] · F. Nicolini[20] · D. Niederwieser[21] · F. Pane[22] · J. P. Radich[23] · D. Rea[24] · J. Richter[25] · G. Rosti[2] · P. Rousselot[26] · G. Saglio[27] · S. Saußele[28] · S. Soverini[2] · J. L. Steegmann[29] · A. Turkina[30] · A. Zaritskey[31] · R. Hehlmann[28,32]

Time	Optimal response
Baseline	
3 mos.	BCR-ABL^{IS} ≤ 10% Ph+ ≤ 35% (PCyR)
6 mos.	BCR-ABL^{IS} < 1% Ph+ 0% (CCyR)

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12 mos.	BCR – $ABL^{IS} \leq 0.1\%$ (MMR)
Then, and at any time	MMR or better

Agent (Brand Name)	Approved Indications
Imatinib mesylate (Gleevec)	All phases
Dasatinib (Sprycel)	All phases
Nilotinib (Tasigna)	All phases except blastic phase
Bosutinib (Bosulif)	All phases except frontline
Ponatinib (Iclusig)	Optimal TKI if T315I mutation failure of ≥ tyrosine kinase inhibitors
Omacetaxine mepesuccinate (Synribo)	Failure ≥ 2 tyrosine kinase inhibitors

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ACUTE BACTERIAL MENINGITIS

- Acute suppurative infection involving subarachnoid space

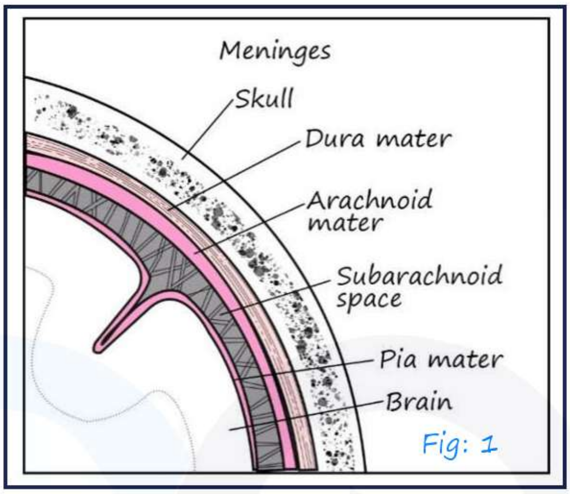

Fig: 1

Organism involved 00:04:45

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Population	Usual microorganisms
18-50years	Streptococcus pneumoniae, Neisseria meningitidis
Over 50years	L monocytogenes, gram-negative bacilli, S pneumoniae
Postsurgical (or) posttraumatic	Staphylococcus aureus, S pneumoniae, aerobic gram-negative bacilli, coagulase-negative staphylococci[5], Diphtheroids (eg, Propionibacterium acnes)[5] (uncommon)

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Causes of bacterial meningitis by route

Route	Bacteria
Infection in (or) around the head (eg. Sinusitis, otitis, mastoiditis), sometimes with a leak of cerebrospinal fluid	Streptococcus pneumoniae Haemophilus influenzae Anaerobic and microaerophilic streptococci Bacteroides species Staphylococcus aureus
Penetrating head wound	S. aureus
Damaged skin (eg, skin infections, abscesses, pressure ulcers, large burns)	S. aureus
An infected shunt	S. epidermidis
A neurosurgical procedure	Gram-negative bacteria (eg, klebsiella pneumoniae, Acinetobacter calcoaceticus, Escherichia coli)

- Neonates and infants
  - E. Coli
  - Group B streptococci
  - Listeria
- E. coli is common <1month
- Childhood
  i. Strep. Pneumoniae
  ii. N. meningitides
    - Incidence of hemophilus influenza meningitis reduced due to vaccination
- Adolescent (11-18 years) → N. meningitides
- N. meningitides
    - Quadrivalent meningococcal vaccine

(Against strains A, C, Y, W-135)

↓

Does not protect against serogroup B

↓

Men B vaccine

- Pneumococcus
  - Virulent
  - Long lasting neurological sequalae
- Listeria
  - Extremes of age
  - Cell mediated immunity defect
  - Pregnancy

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Disease entity	Organisms
Acute bacterial meningitis:	
Age <50 and no risk factors for listeria	Streptococcus pneumoniae, Neisseria meningitidis
Age >50 and/or risk factors for listeria	As above + listeria monocytogenes
Sinusitis, mastoiditis, or otitis predisposing cause of meningitis	As above (depending on age and risk factors) + anaerobes
Brain abscess	Staphylococcus aureus, aerobic and anaerobic streptococci, oral and gastrointestinal flora (including bacteroides spp.) Nocardia
Spinal epidural abscess (SEA)	Staphylococcal spp., Streptococcal spp., enteric gram-negative bacilli
Chronic meningitis or SEA	Mycobacterium tuberculosis (high suspicion)
Neurosyphilis	Treponema pallidum

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Pathophysiology 00:22:28

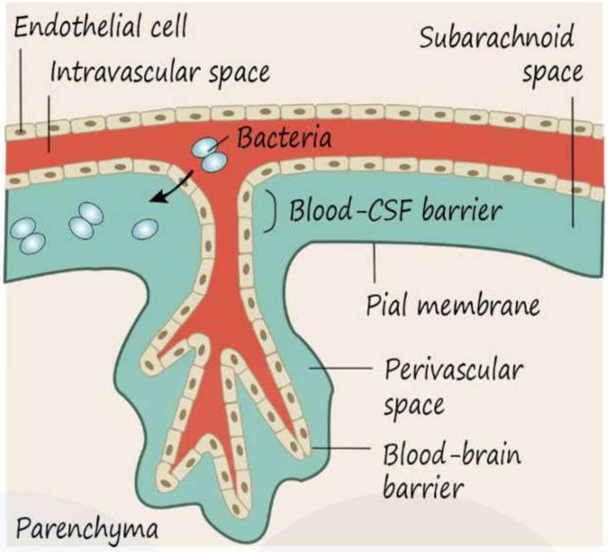


Fig: 2

- Both pneumococcal and listeria are nasopharyngeal colonizers

↓

Nasopharyngeal epithelial cells

↓

Intravascular space

Because of polysaccharide capsule → evade phagocytosis by immune system

↓

Choroid plexus

↓

Subarachnoid space

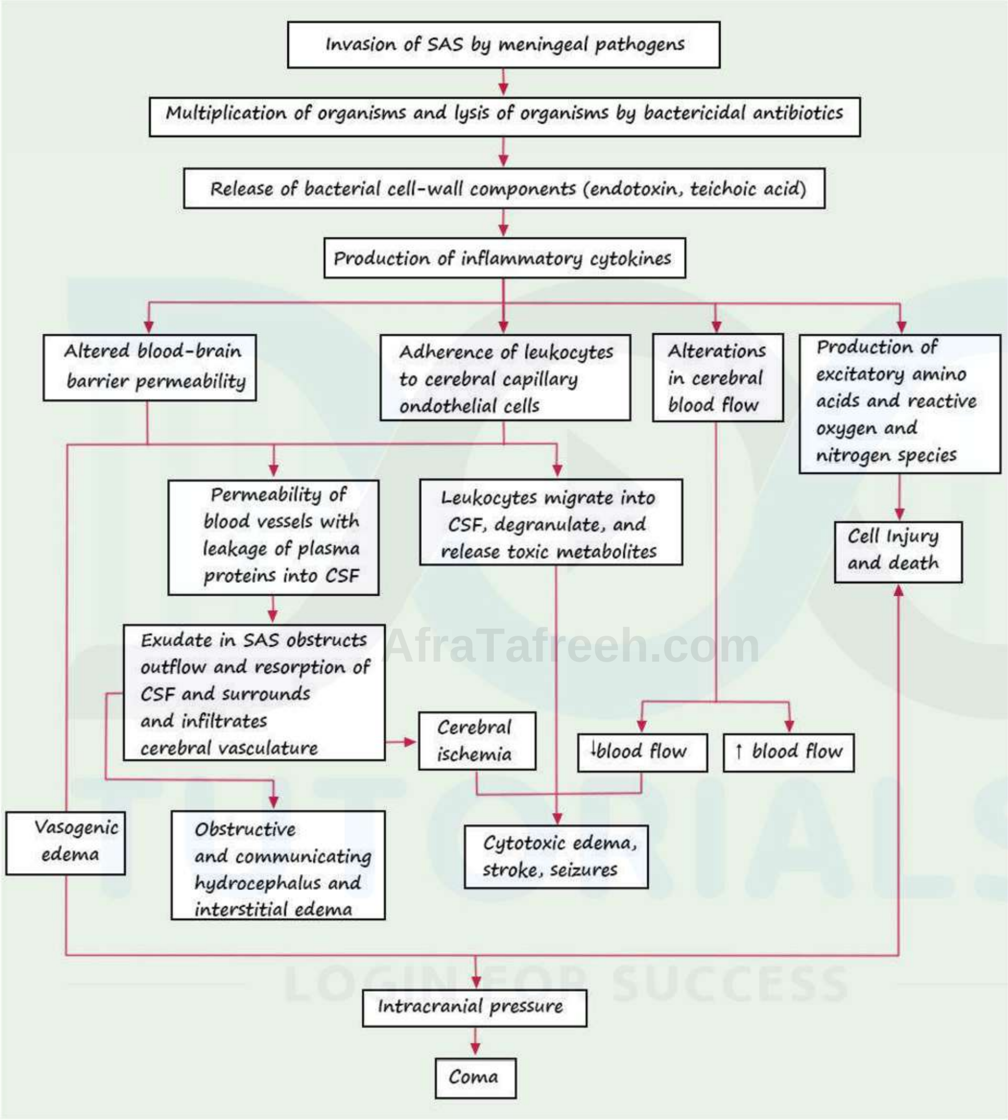
- CSF
  - Very little WBC's
  - No complement
  - No immunoglobulin
- Heavy bacterial load in CSF
- Immune system will produce inflammatory cytokines

↓

TNF-α

IL-1β

- Release of inflammatory cytokines is often triggered by bacterial cell wall products like
  - Techoic acid
  - Endotoxin



- Affection of cerebral arterioles to cerebral infract
- Affection of venous arterioles → venous infract
- Increase intracerebral pressure → cerebral herniation

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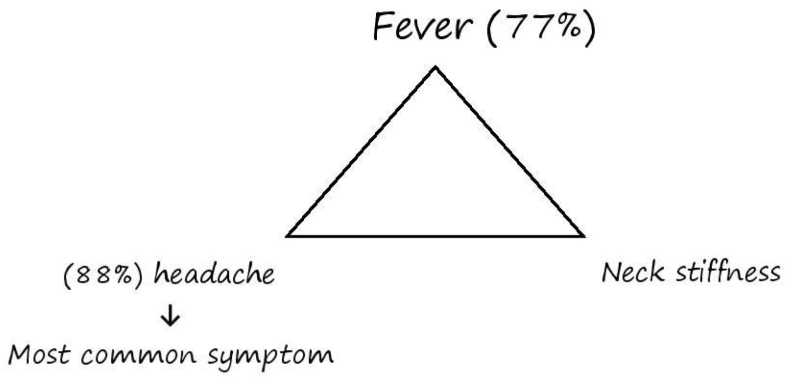
Clinical features 00:42:01

- Classical triad → occurs in hours to days
  (44% of individuals)



- Other symptoms
  - Nausea
  - Vomiting
  - Photophobia
  - Seizures (20-40%)
  - Alteration of consciousness – lethargy → coma
- Increased ICT leads the patient to coma

Features of cerebral herniation

i. Worsening of sensorium

ii. Unilateral (or) bilateral fixed dilated pupils

iii. Decorticate/ decerebrate rigidity

- Patient may develop
  - Vasculitis
  - Cerebral venous thrombosis
  - Subdural empyema
  - Brain abscess
  - Cranial nerve palsies

Complicated meningitis

- Pneumococcal meningitis associated with 8th nerve palsy → SNHL
  - 7th nerve palsy
- Bilateral lateral rectus palsy → false localizing sign

Examination findings 00:53:41

- Signs of meningeal irritation
  - Nuchal rigidity/ neck stiffness
  - Kernig's sign
  - Brudzinski's sign

Fig: 3

Kernig's sign

↓

Position – supine

Hip and knee flexed

Extend knee → meningeal irritation

↓

Pain along hamstrings

↓

Positive Kernig's sign

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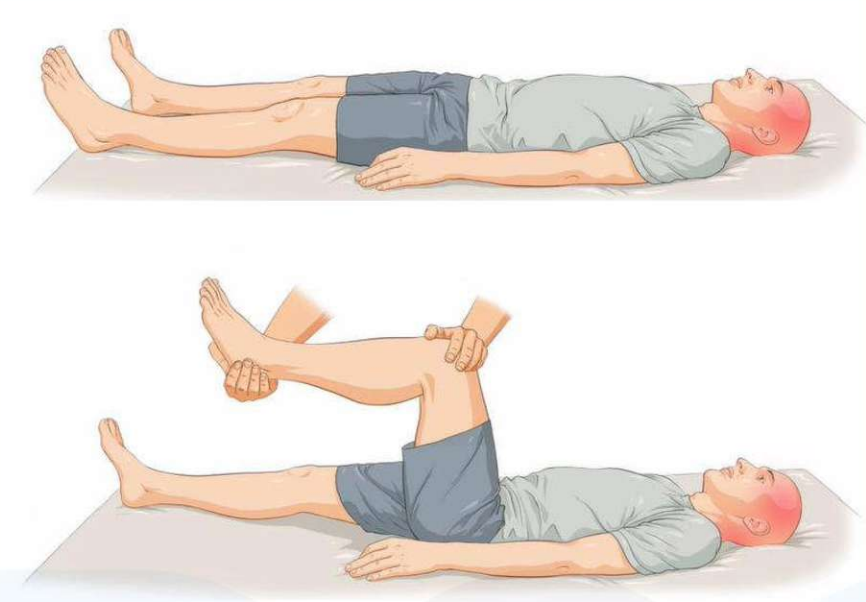

Brudzinski's neck sign Fig: 4

- Position: - Supine
- Examiner will passively flex the neck

  ↓

  Spontaneous flexion of hip and knee of the patient
- Fundus – papilledema
- Bilateral lateral rectus palsy
- Other cranial nerve palsies → 8th nerve → SNHL
- Focal neurological deficits
  - Hemiparesis
  - Aphasia
- Patients with neonatal meningitis will have vague symptoms

  ↓

  Decrease feeds

  Lethargic

  Apnea
- Meningococcal meningitis → petechial rash

↓

Diffuse maculopapular rash

↓

Fulminant meningococcemia

↓

Adrenal hemorrhage

Disseminated Intravascular Coagulation (DIC)

Hypotension

↓

Waterhouse Friedrichsen Syndrome

Fig: 5

Diagnosis 01:03:37

- Clinical suspicion
- Blood cultures
- Lumbar puncture → CSF study
- In case of delay in LP, start antibiotics
- Adjunctive dexamethasone 15-20 mins before giving antibiotics

↓

- Inhibits cytokine release at mRNA level

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- 0.15 mg/kg stat dose f/b (10mg)
- Same dose every 6th hourly x 4days

Lumbar puncture

- Done at $L_3 - L_4$ level
- 21 gauge needle pierced in cephalad direction towards umbilicus
- Structures pierced

- Skin
- Subcutaneous tissue
- Supraspinous ligament
- Interspinous ligament
- Ligamentum flavum
- Dura

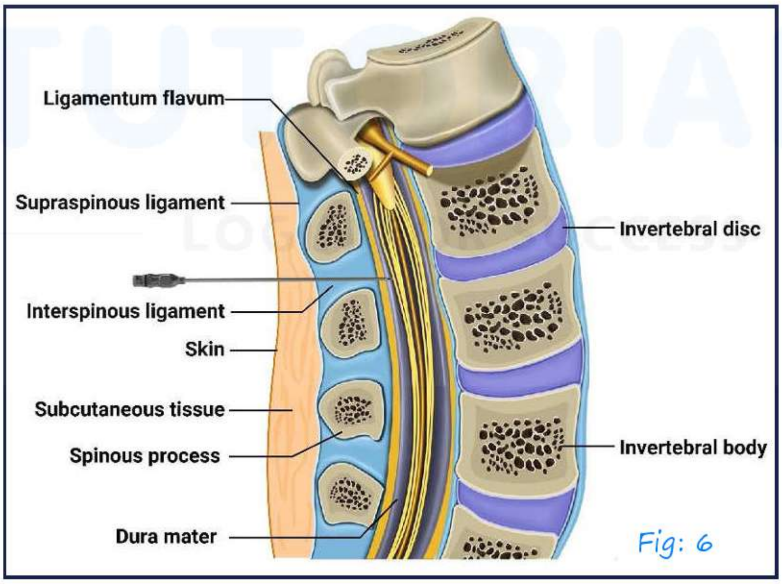

Fig: 6

Cerebrospinal Fluid (CSF) Abnormalities in Bacterial Meningitis	
Opening pressure	>180 mmH_2O
White blood cells	10/μL to 10,000/μL; neutrophils predominate
Red blood cells	Absent in nontraumatic tap
Glucose	<2.2 mmol/L (<40 mg/dL)
CSF/serum glucose	<0.4
Protein	>0.45 g/L (>45 mg/dL)
Gram's stain	Positive in >60%
Culture	Positive in >80%
PCR	Detects bacterial DNA
Latex agglutination	May be positive in patients with meningitis due to Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae type b, Escherichia coli, group B streptococci
Limulus lysate	Positive in cases of gram-negative meningitis

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- In acute bacterial meningitis
  - Polymorphonuclear leucocytosis
  - CSF is turbid
  - CSF sugar <40 mg/dl (Hypoglycorrhachia)
  - CSF/ S. glucose is <0.4
- Normal CSF pressure: - 50-150 mmH_2O

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- Normal CSF WBC: - 0-5
- Normal CSF sugar: - 2/3 of blood sugar
- Normal CSF protein: - 15-45 mg%
  - Latex agglutination test: - high specificity and low sensitivity
  - Limulus lysate: To assess endotoxin of gram-negative bacteria

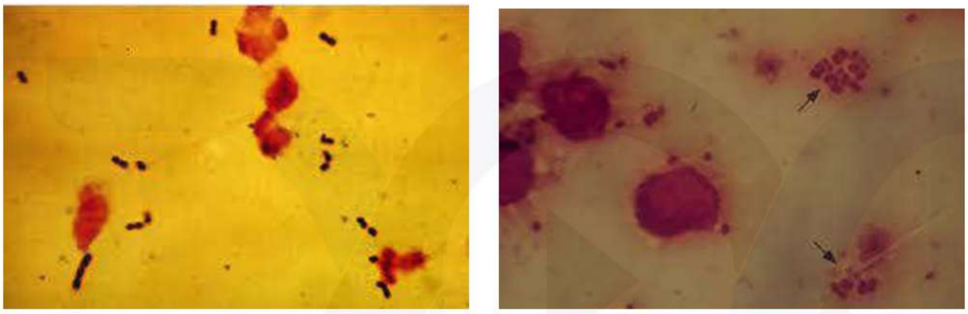

Fig: 7

Clinical risk factors for cerebral herniation

- Stupor (or) coma
- Dilated (or) fixed pupils
- Fixed deviation of eyes (or) absent oculocephalic reflex
- Papilledema
- Recent seizure
- Decorticate (or) decerebrate posturing
- Hemiparesis
- Hypertension with bradycardia

Imaging first than LP

- MRI brain with contrast
- Indications
  - Impaired consciousness
  - Seizures
  - Papilledema
  - Focal neurological deficits
  - Immunocompromised
  - Recent H/O RTA

MRI contrast (Axial view) Fig: 8

In acute bacterial meningitis → Leptomeningeal enhancement

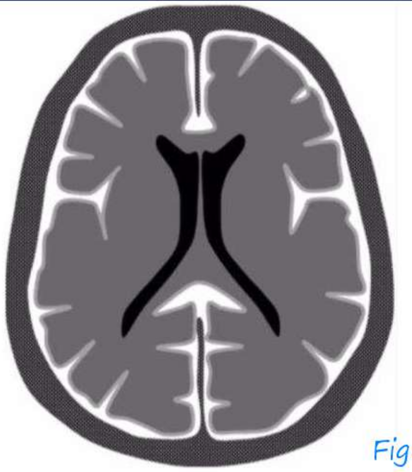

Fig: 9

Leptomeningeal enhancement

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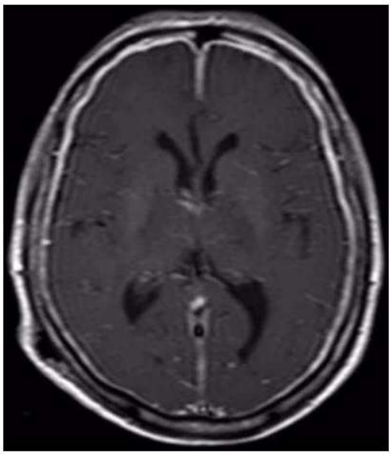

Pachymeningeal enhancement

Egg shell covering the brain Fig: 10

Fig: 11

Pachymeningeal enhancement

Treatment 01:31:45

- Empirical antibiotic therapy

Antibiotics Used in Empirical Therapy of Bacterial Meningitis and Focal Central Nervous System Infections	
INDICATION	**ANTIBIOTIC**
Preterm infants to infants <1 month	Ampicillin + cefotaxime
Infants 1-3 months	Ampicillin + cefotaxime or ceftriaxone
Immunocompetent children >3 months and adults <55	Cefotaxime, ceftriaxone, or cefepime + vancomycin
Adults >55 and adults of any age with alcoholism or other debilitating illnesses	Ampicillin + cefotaxime, ceftriaxone or cefepime + vancomycin
Hospital-acquired meningitis, posttraumatic or post neurosurgery meningitis, neutropenic patients, or patients with impaired cell mediated immunity	Ampicillin + ceftazidime or meropenem + vancomycin

- Otitis media
- Sinusitis

(Otitis media, Sinusitis) — Add metronidazole

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Antimicrobial Therapy of Central Nervous System Bacterial Infections Based on Pathogen	
ORGANISM	**ANTIBIOTIC**
Neisseria meningitides	
Penicillin-sensitive Penicillin-resistant	Penicillin G or ampicillin Ceftriaxone or cefotaxime
Streptococcus pneumoniae	
Penicillin-sensitive Penicillin-intermediate Penicillin-resistant	Penicillin G Ceftriaxone or cefotaxime or cefepime Ceftriaxone (or cefotaxime or cefepime) + vancomycin
Gram-negative bacilli (except Pseudomonas spp.)	Ceftriaxone or cefotaxime
Pseudomonas aeruginosa	Ceftazidime or meropenem
Staphylococci spp.	
Methicillin-sensitive Methicillin-resistant	Nafcillin Vancomycin
Listeria monocytogenes	Ampicillin + gentamicin
Haemophilus influenzae	Ceftriaxone or cefotaxime or cefepime
Streptococcus agalactiae	Penicillin G or ampicillin
Bacteroides fragilis	Metronidazole
Fusobacterium spp.	Metronidazole

Antimicrobial agent	Total daily dose and dosing interval	
	Child (>1 month)	Adult
Ampicillin	300 (mg/kg)/d, q6h	12 g/d, q4h
Cefepime	150 (mg/kg)/d, q8h	6 g/d, q8h
Cefotaxime	225-300 (mg/kg)/d, q6h	12 g/d, q4h
Ceftriaxone	100 (mg/kg)/d, q12h	4 g/d, q12h
Ceftazidime	150 (mg/kg)/d, q8h	6 g/d, q8h
Gentamicin	7.5 (mg/kg)/d, q8h[b]	7.5 (mg/kg)/d, q8h
Meropenem	120 (mg/kg)/d, q8h	6 g/d, q8h
Metronidazole	30 (mg/kg)/d, q6h	1500-2000 mg/d, q6h
Nafcillin	100-200 (mg/kg) d, q6h	9-12 g/d, q4h
Penicillin G	400,000 (U/kg)/d, q4h	20-24 million U/d, q4h
Vancomycin	45-60 (mg/kg)/d, q6h	45-60 (mg/kg) d, q6-12hb

Duration of antibiotics

- Meningococci, H. Influenzae – 7days
- Pneumococcus → 10-14days
- Listeria → 14-21 days
- Gram negative bacilli → 3weeks

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Supportive management

- Fluid and electrolyte status
- Look for features of increase ICT
  - Intubate
  - 30° propped up
  - Hyperventilate
  - 3% saline

Antibiotic	Dose	Duration
Rifampicin	Child <1 month of age: 5 mg/kg 2 times a day orally Child 23 months to 12 years of age: 10 mg/kg 2 times a day orally Child 12 years: 600 mg 2 times a day orally Nonpregnant adult: 600 mg 2 times a day orally	2 Days
Ciprofloxacin	Adult 18 years: 500 mg orally Pregnant: do not use	Once
Ceftriaxone	Child <15 years: 125 mg IM Adult 216 years: 250 mg IM Pregnant: 250 mg IM	Once

- Post RTA → H/O CSF rhinorrhea

↓

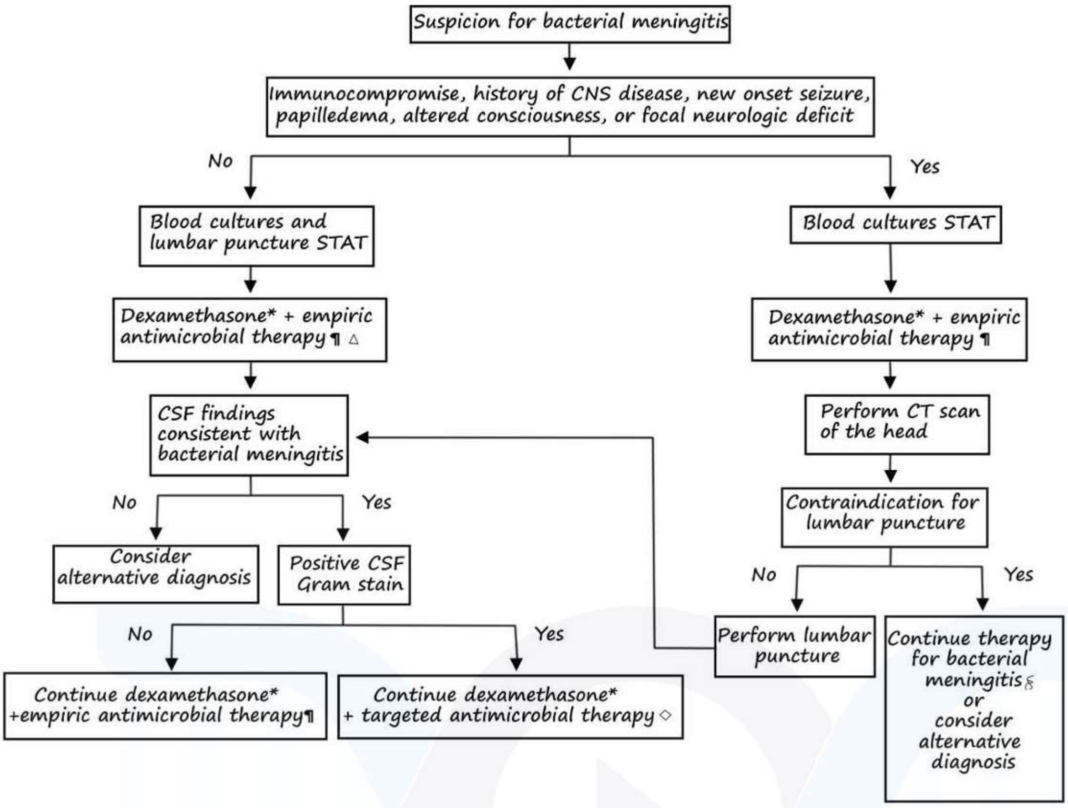
- Fracture of cribriform plate
- Dural tear

→ Recurrent meningitis

↓

HRCT

Radionuclide cisternography



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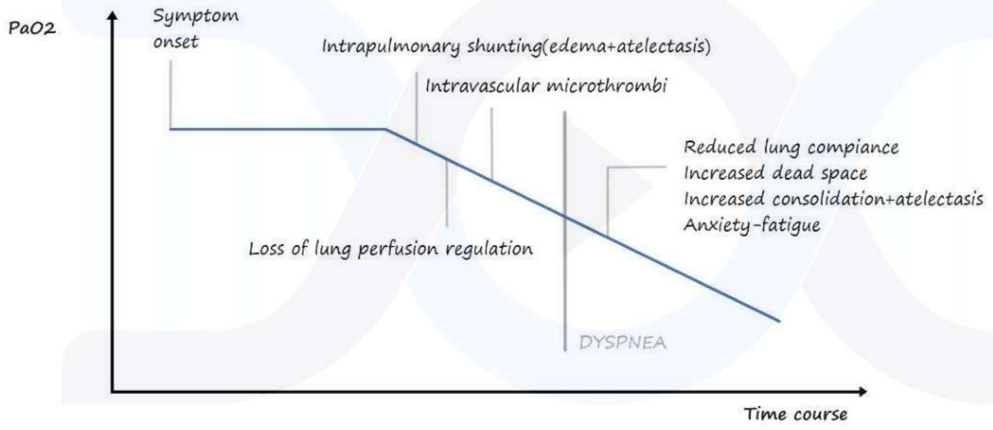
OXYGEN THERAPY IN COVID 19 PATIENTS

- Due to pulmonary involvement, patients may develop
  - Hypoxemia
  - Type I respiratory failure

Mechanism of hypoxemia in COVID 19 patients

00:01:58



- The phase where there was decrease in $PaCo_2$ without dyspnea is amenable to O_2 therapy
- Beyond this phase, we might require mechanical ventilation

Assessment of respiratory distress 00:07:05

- Symptoms – Dyspnea, tachypnea, chest tightness
- Work of breathing
- SpO2 – Peripheral oxygen saturation
- Partial pressure of arterial oxygen (PaO2)
  - P/F ration – PaO2/FiO2 ratio

- S/F ratio (SaO2/FiO2)
  - S/F ratio of 235 =
  - S/F ratio of 315 =
- Work of breathing – accessory muscles of respiration

↓

Flaring of alae nasi

Sternocleidomastoid

Intercostal retraction

- S/F ratio of 235 = P/F ratio of 200
- S/F ratio of 315 = P/F ratio of 300

Sa O_2 target? 00:11:40

- If the patient is in ward: – 92–94%
  - ICU: – 90–92%

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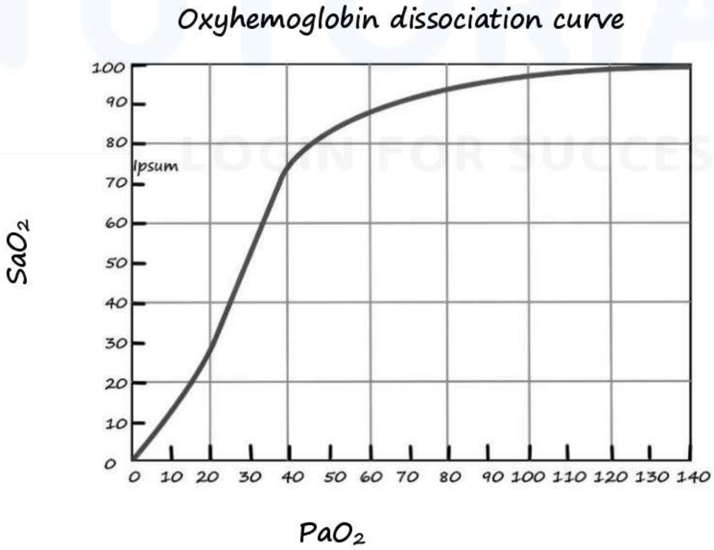
O_2 dissociative curve 00:12:40



- Once the saturation is around 90–92, if you increase O_2 support also, it is not much effective
- Hyperoxemia → Free radical species formation

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Oxygen delivery devices 00:14:50

- Conventional oxygen therapy
  - Variable performance systems/low flow
  - Fixed performance systems/high flow
- High flow nasal oxygenation
- Noninvasive ventilation

Conventional oxygen therapy 00:16:22

- Depending on amount of inspired gas, it supplies
- System provides all the patient's inspired gas, stable FiO_2 – High flow system
- System provides low flow; patient draws remaining from surrounding air – low flow system

Low flow systems 00:18:28

Nasal cannula

Fig: 1

- Flow: 1-6L/min
- FiO_2: 24-44% (0.24-0.44)

Hudson's O_2 mask

Fig: 2

- Max FiO_2 – 60%

NRBM

Fig: 3

- Non rebreathing mask
- FiO_2: 80-95%
- Consists of face mask and reservoir bag
- Between the mask and reservoir bag, there is one way value
- The reservoir bag should always be inflated (capacity-IL)
- To achieve this inflation, get a flow rate of 10L/minute

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High flow systems 00:22:54

Venturi mask

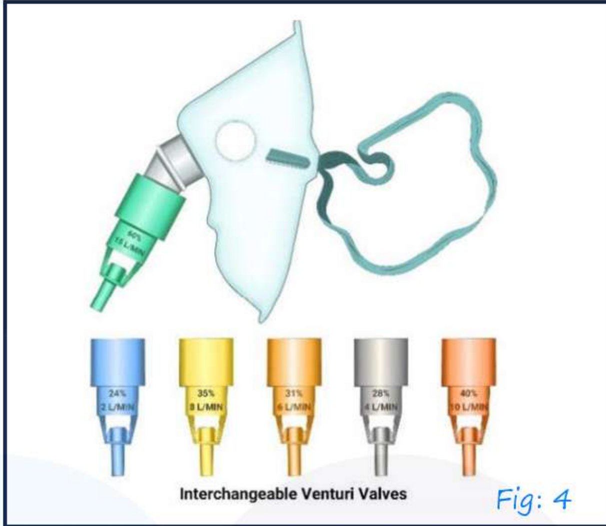

Fig: 4

- Venturi mask is based on venturi principle
- Venturi devices are color coded
- FiO_2 attained will depend on the venturi value and flow rate
- Green – 60% FiO_2
- Blue – 24% FiO_2

High flow nasal oxygenation 00:25:58

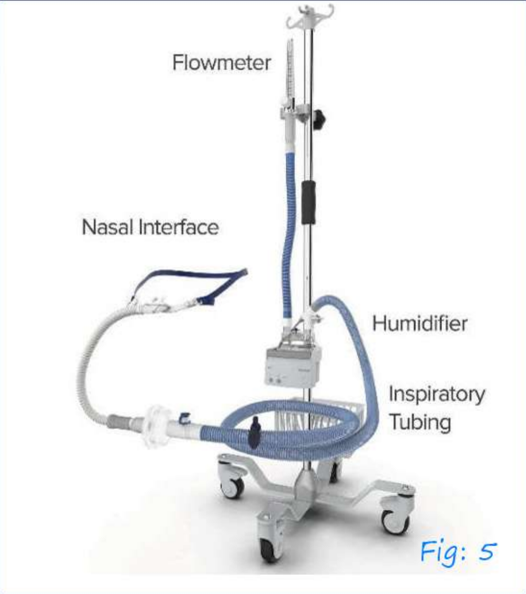

Fig: 5

- Consists of
  - Flow meter – O_2 source
  - Blender – mix O_2 and air (FiO_2: - 21% - 100%)
  - Humidifier – warm and humidified air
  - Nasal interface
  - Inspiratory tubing

Physiological effects of HFNO

- Heated humidified air at high flow and delivers high FiO_2
- Heating and humidification
  - Preserves mucociliary clearance and helps clear respiratory secretions
- Improves oxygenation and reduces dead space
- High flow – produces high expiratory impendence
  - Generates an extrinsic PEEP of 4-6 cm H_2O and lower respiratory rate and work of breathing

Techniques of HFNC

- Fit the nasal prongs
- Put surgical mask to reduce aerosol dispersion
- Initiate maximum flow (60L/min – 80L/min)
- Adjust FiO_2 as per saturation
- For humidification – Start with 37 deg C and adjust down 34 deg C

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Monitoring of HFNC

- Respiratory rate, breathing pattern, SPO_2

$$\text{ROX index} = \frac{SPO_2/FiO_2}{\text{Respiratory rate}}$$

Respiratory rate – Oxygenation

Predictor of HFNC failure

- ROX <2.85 at 2hours
- ROX <3.47 at 6hours
- ROX <3.85 at 12hours

Non invasive ventilation 00:25:58

- Positive pressure is generated in airways
  - Either by a standalone device or via ventilator
  - Delivered by an interface (full face mask, nasal mask)
- 2 types
  - CPAP – Continuous positive pressure throughout respiratory cycle
  - BiPAP – Varying positive pressure during inspiration and expiration

Full face mask

Nasal mask

Helmet device

Fig: 6

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Technique of NIV

- Start with of 10cm H_2O and PSV of 15cm H_2O and titrate to RR <20/min
- Start with FiO_2 of 1 and down titrate to maintain SpO_2 92-94%
- NIV monitoring – RR, SpO_2, breathing pattern, ABG

Problems with NIV

- Risk of aspiration
- Claustrophobia
- Excessive tidal volume – Lung injury
- Higher mortality in patients with P/F < 150

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Contraindications to NIV

- Altered level of consciousness
- Agitated, un co-operative (or) restless patient
- Copious respiratory secretions
- Persistent vomiting
- Hemodynamic instability

Prone positioning

- Increases pulmonary compliance
- Improves gas exchange
- Homogenizes lung aeration

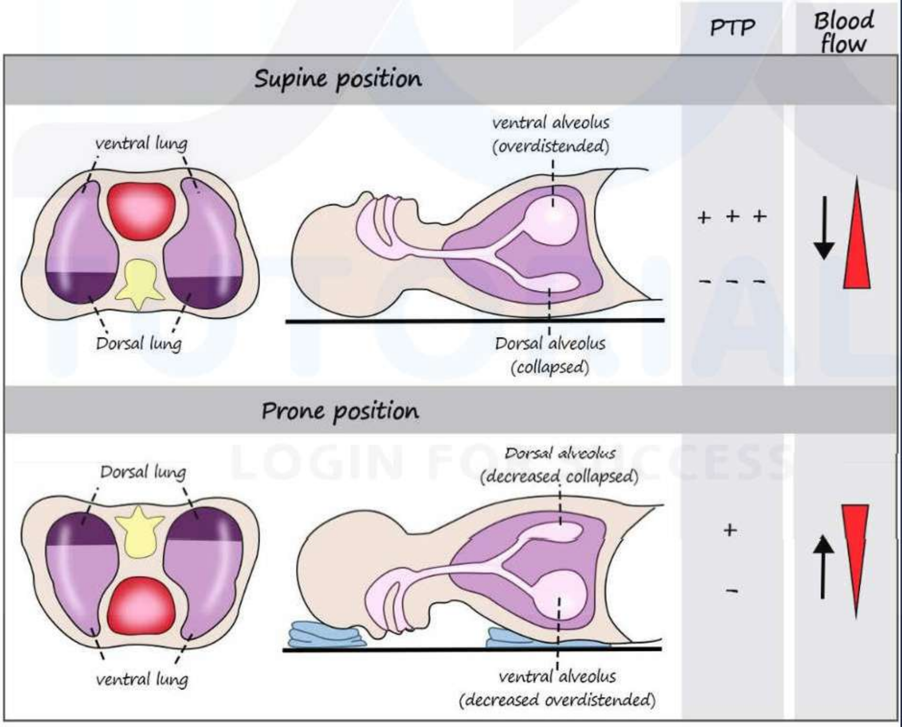

Fig: 7

- Transpulmonary pressure – Distending pressure of alveoli

- Difference in transpulmonary pressure of ventral and distal alveolus is more

↓

Ventral alveolus is over distended and dorsal alveolus is collapsed

- In prone position → Difference between transpulmonary pressure reduced
- Ventilation perfusion matching is decreased in prone position
- V/Q mismatch – perfusion mismatch occurs in supine position

↓

Maximum blood flow to collapsed alveoli

Minimum blood flow to overdistended alveoli

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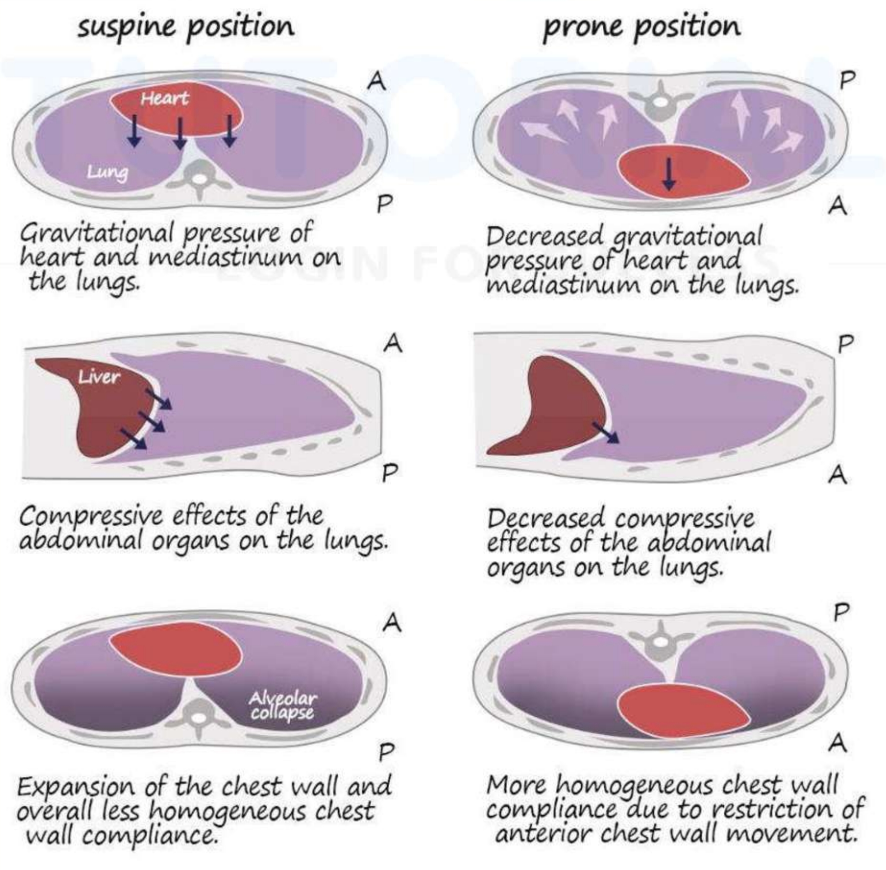

Fig: 8

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Positioning of pillow

- One pillow below the neck
- One (or) two pillows below the chest through upper thighs
- Two pillows below the shins

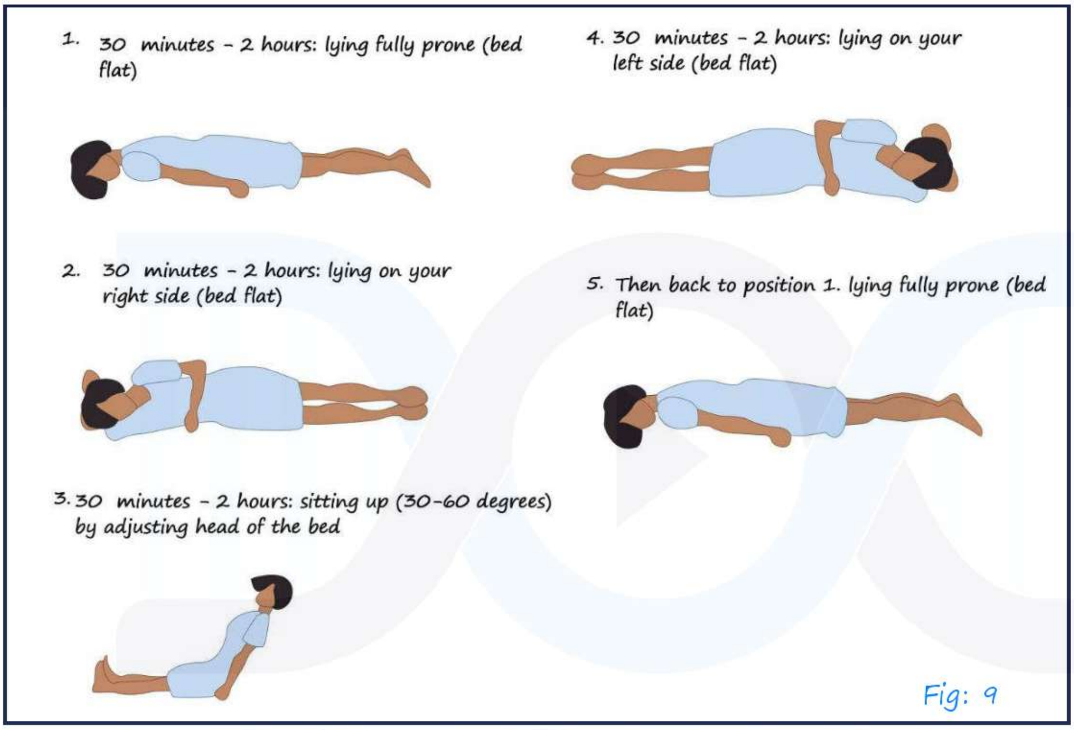

Fig: 9

Determination of need for endotracheal intubation for COVID-19-Related respiratory failure

i. Possible clinical indications of endotracheal intubation

- Impending airway obstruction
- Signs of unsustainable work of breathing
- Refractory hypoxemia
- Hypercapnia (or) acidemia
- Encephalopathy (or) inadequate protection

ii. Additional considerations

- Does illness trajectory predict deterioration?
- Are difficulties in endotracheal intubation anticipated?
- Is there hemodynamic instability?
- Will intubating now improve the safety of a planned procedure (or) transportation?
- Will intubating now improve infection control and staff safety

Fig: 10

Algorithm for oxygen management 00:52:02

Step 1

- No respiratory distress
- SpO_2 < 92-94% RA (or) declining SpO_2

↓

Simple oxygen supplementation

O_2 via N/C @ 4-6 L/min

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Step 2

- Mild to moderate respiratory distress
- 150 > P/F < 300 (or) Spo_2 <90-94% on NRB mask and/or labored breathing; hemodynamically stable

Noninvasive strategies

Transfer to continuously monitored setting

Observe patient closely and obtain ABG in 30min

High flow nasal cannula	**Awake Proning**	**Noninvasive ventilation**
(Preferred modality) Minimal hypercapnia ($Paco_2$ preferably < 5mm Hg above baseline)	(Alone or with HFNC or NIV) Useful with diffuse lung opacities ARDS No unstable spine fractures, hemoptysis, abdominal compartment syndrome, > first trimester pregnancy, anterior chest tubes	(Consider helmet) COPD with moderate hypercapnia or cardiogenic pulmonary edema or inability to carry out work of breathing Low aspiration risk

Step 3

- No respiratory distress
  - P/F <150 or
  - SpO_2/PaO_2 <196 or
  - Hemodynamically unstable (or) at risk of impending respiratory arrest

Invasive Mechanical Ventilation

(Unless carries a Do Not Intubate order)

ARDS net guidelines.

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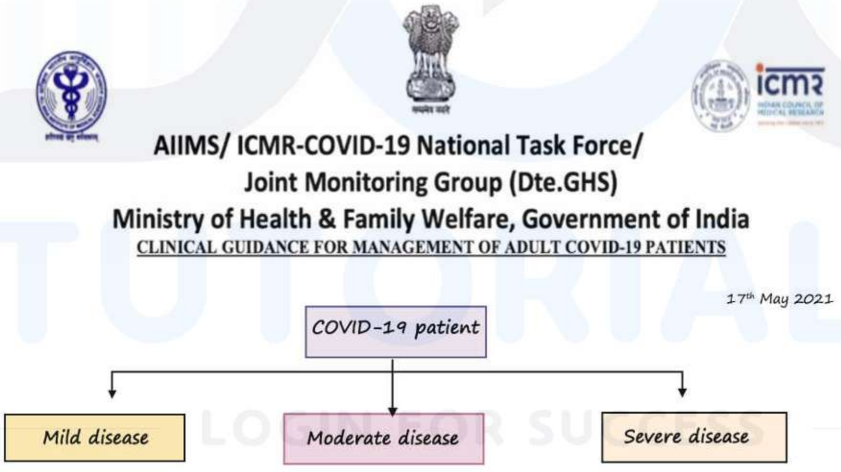
MANAGEMENT OF COVID – 19

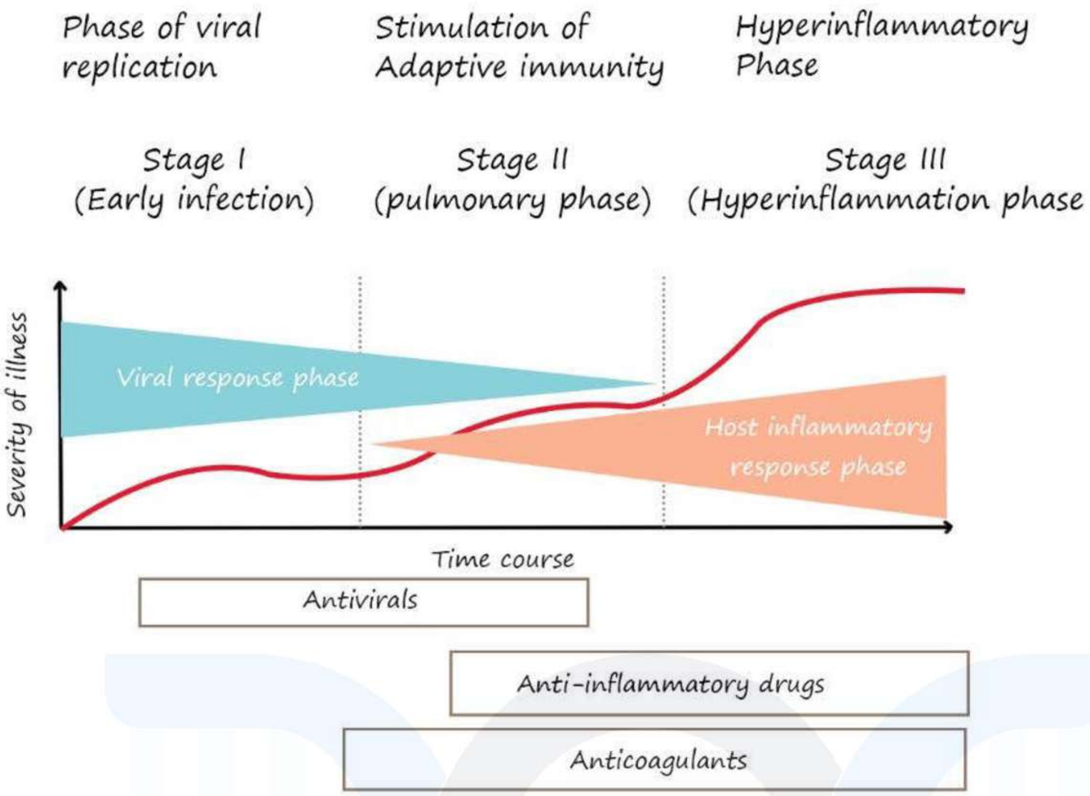
- Oxygen
- Steroids
- Anticoagulants
- Antivirals
- Monoclonal antibodies
  - National guidelines are by AIIMS – ICMR National Task Force

AIIMS – ICMR Guidelines 00:05:25



Spectrum of disease manifestations 00:07:19

- 85% – Asymptomatic or mild disease
- 15% – Moderate to severe disease
- 5% – Require critical care management in ICU
- According to Indian data, 3% require critical care management in ICU



Covid – 19 patients

Mild disease	Moderate disease	Severe disease
Upper respiratory tract symptoms (&/or fever) without shortness or breath or hypoxia	Any one of: 1. Respiratory rate $\geq$ 24/min, breathlessness 2. SpO_2: 90% to $\leq$ 93% on room air	Any one of: 1. Respiratory rate >30/min, breathlessness 2. SpO_2 <90% on room air

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Mild Covid – 19 Definitions 00:13:32

- The asymptomatic cases are laboratory confirmed cases not experiencing any symptoms and having oxygen saturation at room air of more than 94%
- Clinically assigned mild cases are patients with upper respiratory tract symptoms (&/or fever) without shortness of breath and having oxygen saturation at room air of more than 94%.

Mild Disease

Upper respiratory tract symptoms (&/or fever) without shortness of breath or hypoxia

Home Isolation & Care

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Home Isolation 00:15:21

Patients eligible for home isolation

- The patient should be clinically assigned as mild/asymptomatic case by the treating medical officer.
- Such cases should have the requisite facility at their residence for self-isolation and for quarantining the family contacts.

- A care giver should be available to provide care on 24x7 basis. A communication link between the caregiver and hospital is a prerequisite for the entire duration of home isolation.
- Elderly patients aged more than 60 years and those with Co-morbid conditions such as hypertension, diabetes, heart disease, chronic lung/liver/kidney disease, Cerebro-vascular disease etc. shall only be allowed home isolation after proper evaluation by the treating medical officer.
- Patients suffering from immune compromised status (HIV, transplant recipients, cancer therapy etc.) are not recommended for home isolation and shall only be allowed home isolation after proper evaluation by the treating medical officer

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Must Dos

- Physical distancing, indoor mask use, strict hand hygiene.
- Symptomatic management (hydration, anti-pyretics, anti-tussive, multivitamins).
- Stay in contact with treating physician.
- Monitor temperature and oxygen saturation (by applying a SpO_2 probe to fingers).
- Pulse oximeter
  - Placed for minimum of 1 minute
  - Stable value for 5 seconds

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- Seek immediate medical attention if
  - Difficulty in breathing
  - High grade fever/severe cough, particularly if lasting for >5 days
  - A low threshold to be kept for those with any of the high-risk features.

High risk factors 00:25:12

High risk for severe disease or mortality

- Age > 60 years
- Cardiovascular disease, hypertension, and CAD
- DM (Diabetes mellitus) and other immunocompromised states
- Chronic lung/kidney/liver disease
- Cerebrovascular disease
- Obesity

May Dos 00:25:51

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Therapies based on low certainty of evidence

- Tab ivermectin (200 mcg/kg once a day for 3 days). Avoid in pregnant and lactating women.

  Or

- Tab HCQ (400 mg BD for 1 day f/b 400 mg OD for 4 days) unless contraindicated.

- Inhalational Budesonide (given via metered dose inhaler/Dry powder inhaler) at a dose of 800 mcg

BD for 5 days) to be given if symptoms (fever and/or cough) are persistent beyond 5 days of disease onset.

Instructions to patients 00:29:03

- Patient must isolate himself from other household members, stay in the identified room and away from other people in home, especially elderlies and those with co-morbid conditions like hypertension, cardiovascular disease, renal disease etc.
- The patient should be kept in a well-ventilated room with cross ventilation and windows should be kept open to allow fresh air to come in.
- Patient should at all times use triple layer medical mask. Discard mask after 8 hours of use or earlier if they become wet or visibly soiled. In the event of care giver entering the room, both care giver and patient may consider using N 95 mask.
- Mask should be discarded only after disinfecting it with 1% sodium hypochlorite.
- Patient must take rest and drink lot of fluids to maintain adequate hydration.
- Follow respiratory etiquettes at all times.
- Frequent hand washing with soap and water for at least 40 seconds or clean with alcohol-based sanitizer.

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- Don't share personal items with other people in the household.
- Ensure cleaning of surfaces in the room that are touched often (tabletops, doorknobs, handles, etc.) with 1% hypochlorite solution.
- Self-monitoring of blood oxygen saturation with a pulse oximeter is strongly advised.
- The patient will self-monitor his/her health with daily temperature monitoring and report promptly if any deterioration of symptom as given below is noticed.

Day of symptoms and time (every 4 hourly)	Temperature	Heart rate (from pulse oximeter)	SpO_2% (from pulse oximeter)	Feeling: (better/ same/ worse)	Breathing: (better/ same/ worse)

Instructions to caregiver

- The caregiver should wear a triple layer medical mask. N95 mask may be considered when in the same room with the ill person.
- Front position of the mask should not be touched or handled during use.
- If the mask gets wet or dirty with secretions, it must be changed immediately.
- Discard the mask after use and perform hand hygiene after disposal of the mask.

- Hand hygiene must be ensured following contact with ill person or his immediate environment.
- Hand hygiene should also be practiced before and after preparing food, before eating, after using the toilet, and whenever hands look dirty.
- Use soap and water for hand washing at least for 40 seconds. Alcohol based hand rub can be used, if hands are not visibly soiled.
- After using soap and water, use of disposable paper towels to dry hands is desirable. If not available, use dedicated clean towels and replace them when they become wet.
- Perform hand hygiene before and after removing gloves.
- Avoid direct contact with body fluids of the patient, particularly oral or respiratory secretions. Use disposable gloves while handling the patient.
- Avoid exposure to potentially contaminated items in his immediate environment (e.g. avoid sharing cigarettes, eating utensils, dishes, drinks, used towels or bed linen).
- Food must be provided to the patient in his room. Utensils and dishes used by the patient should be cleaned with soap/detergent and water wearing gloves. The utensils and dishes may be re-used.
- Clean hands after taking off gloves or handling used items. Use triple layer medical mask and disposable

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gloves while cleaning or handling surfaces, clothing or linen used by the patient.

- Perform hand hygiene before and after removing gloves.

Discontinuation of home isolation 00:37:34

- Patient under home isolation will stand discharged and end isolation after atleast 10 days have passed from onset of symptoms (or from date of sampling for asymptomatic cases) and no fever for 3 days. There is no need for testing after the home isolation period is over.

Moderate Covid-19 00:39:17

- RR – 24-30/min, breathlessness

  (or)

- SPO_2 – 90-93%

Management

i. Admit in ward

ii. Oxygen → target SPO_2 → 92-96%

COPD ⊕ → 88-92%

Encourage awake proning

iii. Steroids – Methylprednisolone [0.5 – 1mg/kg iv 2 divided doses 5-10 days]

(or)

Dexamethasone

Oral steroids when stable

iv. Anticoagulation – LMWH or UFH

Enoxaparin – 0.5 mg/kg S.C OD

v. Supportive – Hydration

Antipyretics

Anti-tussive

Admit in ward

- Oxygen support:
  - Target SpO_2: 92-96% (88-92% in patients with COPD).
  - Preferred devices for oxygenation: non-rebreathing face mask.
  - Awake proning encouraged in all patients requiring supplemental oxygen therapy (sequential position changes every 2 hours).
- Anti-inflammatory or immunomodulatory therapy
  - Inj. Methylprednisolone 0.5 to 1 mg/kg in 2 divided doses (or an equivalent dose of dexamethasone) usually for a duration of 5 to 10 days.
  - Patients may be initiated or switched to oral route if stable and/or improving.
- Anticoagulation
  - Conventional dose prophylactic unfractionated heparin or low molecular weight heparin (weight

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based e.g., enoxaparin 0.5 mg/kg per day SC). There should be no contraindication or high risk of bleeding.

Monitoring – moderate Covid-19

- Clinical
  - Work of breathing
  - Hemodynamic status
  - Changing oxygen requirement
- Lab
  - CXR
  - HRCT
  - CBC, LFT, RFT (24-48 hours)
  - CRP, D-dinner (48-72 hours)
  - IL-6

- Monitoring
  - Clinical monitoring: work of breathing, hemodynamic instability, change in oxygen requirement.
  - Serial CXR; HRCT chest to be done only if there is worsening.
  - Lab monitoring: CRP and D-dimer 48 to 72 hrly; CBC, KFT, LFT 24 to 48 hrly; IL-6 levels to be done if deteriorating (subject to availability).

- RR – 30/min, breathlessness

  (or)

- SPO_2 < 90%

Management

i. Admit in ICU

ii. Oxygen – HFNO/NIV/Mechanical ventilation

iii. Steroids – Methylprednisolone (1-2 mg/kg iv 2 divided doses 5-10 days)

(or)

Dexamethasone

iv. Anticoagulation – UFH or LMWH

Enoxaparin – 0.5 mg/kg S.C BD

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Admit in ICU

- Respiratory support
  - Consider use of NIV (Helmet or face mask interface depending on availability) in patients with increasing oxygen requirement, if work of breathing is LOW.
  - Consider use of HFNC in patients with increasing oxygen requirement.
  - Intubation should be prioritized in patients with high work of breathing/if NIV is not tolerated.

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- Use conventional ARDSnet protocol for ventilatory management.

- Anti-inflammatory or immunomodulatory therapy
  - Inj methylprednisolone 1 to 2mg/kg IV in 2 divided doses (or an equivalent dose of dexamethasone) usually for a duration 5 to 10 days.
- Anticoagulation
  - Weight based intermediate dose prophylactic unfractionated heparin or low molecular weight heparin (e.g., enoxaparin 0.5 mg/kg per dose SC BD). There should be no contraindication or high risk of bleeding.

Monitoring COVID-19

- CBC, LFT, RFT → daily
- CRP, D-dimer (24-48 hours)
- CXR
- HRCT
- Serial CXR; HRCT chest to be done only if there is worsening.
- Lab monitoring: CRP and D-dimer 24-48 hourly; CBC, KFT, LFT daily; IL-6 to be done if deteriorating (subject to availability).

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Remedesivir

- Inhibitor of RNA dependent RNA polymerase, which is essential for viral replication
- It is an adenosine nucleotide prodrug that is metabolized to the pharmacologically active nucleoside triphosphate metabolite after being distributed into cells
- May be considered in patients with
  - Moderate to severe disease (required oxygen)
  - Within 10days of onset of symptoms

Remdesivir – Dosing

- 200mg iv as single dose on Day 1, followed by;
  - 100 mg iv OD for 5days
- The iv dosage is given over 30-120min
- Usually given for 5days, can be extended up to 10 days, if no substantial improvement by Day 5

Remdesivir – Side effects

- Nausea
- Skin rash
- Hypersensitivity reactions
- Severe bradycardia
- Hypotension
- Deranged LFT

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Remdesivir – Contraindications

- Hepatic dysfunction (AST/ALT >5times ULN)
- Renal impairment (GFR <30ml/min)
- Pregnancy, lactation
- Children <12 years
- History of hypersensitivity to remdesivir or any component of the formulation

Advisory for rational use of remdesivir for COVID-19 treatment MOHFW 2021

- Remdesivir is to be used only in select moderate/ severe hospitalized Covid-19 patients on supplemental oxygen as it is a reserve drug approved under emergency use authorization only based on limited scientific evidence globally
- It is not indicated in mild Covid-19 patients who are in home care/ covid care centers
- Remdesivir (EUA) may be considered ONLY in patients with
  - Moderate to severe disease (required SUPPLEMENTAL OXYGEN), AND
  - No renal or hepatic dysfunction (eGFR <30ml/min/m^2; AST/ALT >5times ULN (Not an absolute contradiction), AND
  - Who are within 10 days of onset of symptom/s
  - Recommended dose: 200mg IV on day 1 f/b 100mg IV OD for next 4days

- Not be used in patients who are NOT on oxygen support or in home settings

Favipiravir

- Inhibitor of RNA dependent RNA polymerase, which is essential for viral replication
- Antiviral drug used to treat influenza
- At present, found to have no effect on mortality (or) severity in COVID-19 patients
- Can leads to teratogenicity, transaminitis, neutropenia and dose dependent hyperuricemia

Lopinavir – Ritonavir

- Co-formulation of lopinavir and ritonavir
- At present, found to have no effect on mortality (or) severity in COVID-19 patients

Ivermectin

- Semisynthetic anti-helminthic agent
- "May be" given in mild COVID-19
- Dose: 200 mcg/kg once daily for 3 days
- No dose adjustment needed in hepatic (or) renal impairment

Ivermectin

- Contraindication
  - Hypersensitivity to ivermectin

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- Pregnancy and lactation
- Side effects
  - Pruritus, rash, arthralgia, synovitis, edema nausea, diarrhea, tachycardia, increased ALT/AST
- Don't combine ivermectin with azithromycin

Convalescent plasma 01:16:15

- Proposed mechanism – It contains antibodies to SARS-CoV-2, that may help to suppress the virus and modify the inflammatory response
- Initial case series shoed promising results, but RCT's have not demonstrated efficacy and hence not in guidelines

Immunomodulators 01:16:15

- Anti-IL-6 drugs
- Anti-IL-6 receptor monoclonal antibodies
  - Tocilizumab
  - Sarilumab
- Anti-IL-6 monoclonal antibodies
  - Siltuximab
- JAK inhibitors
  - Barcitinib

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Tocilizumab

- Inhibits binding of IL-6 to IL-6 receptor

- When to consider? – All the following should be met
  - Rapid deterioration/ presence of severe disease
  - Ideally within 24-48 hours of onset of severe disease
  - Not improving despite use of steroids
  - Significantly raised inflammatory markers (CRP, IL-6)
  - No active bacterial/ fungal/ tubercular infection
- Dose: 4-6 mg/kg (400 mg in 60kg adult) in 100 ml NS over 1 hours
- Adverse effects
  - Infusion related allergic reactions
  - Deranged LFT
  - Late onset secondary infections
  - Severe disseminated strongyloidiasis (steroids + tocilizumab)
- Tocilizumab (Off-label) may be considered when ALL OF THE BELOW CRITERIA ARE MET
  - Presence of severe disease (preferably within 24 to 48hour of onset of severe disease/ ICU admission)
  - Significantly raised inflammatory markers (CRP and/or IL-6)
  - Not improving despite use of steroids
  - No active bacterial/ fungal/ tubercular infection
  - Recommended single dose: 4 to 6 mg/kg (400 mg in 60kg adult) in 100ml NS over 1 hour

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Baricitinib

- Mechanism – Blockers signaling via numerous cytokines including IL-2, IL-6, IL-12 and interferons
- Not in the guidelines

Infections for JAK inhibitors in COVID 19

- Diagnosed COVID 19 infection
  i. Consider only for patients who have not received tocilizumab (or) on mechanical ventilation, who require 8L O2 (or) FiO2 > 0.4 (or) higher levels of respiratory support for at least 8 hours and are improving despite 24 hours of standard care including dexamethasone
  ii. In rare circumstance when corticosteroids cannot be used, baricitinib (or) tofacitinib may be used for the treatment of COVID-19 in hospitalized, non-intubated patients who require oxygen supplementation
- Baricitinib (or) tofacitinib should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus
- Dose: Baricitinib – Oral 4 mg once daily
- Tofacitinib – Oral 10mg twice a day
  - Duration of baricitinib and tofacitinib is 7 to 14 days based on clinical response (or) until hospital discharge

Baricitinib

- Contraindications
  - Absolute neutrophil count <500 cells/mm^3
  - Active severe infection
  - Substantial immune dysfunction
  - Severe renal failure
  - Pregnancy
- Complications
  - Immunosuppression
  - Cytopenia
  - Thromboembolic effects – PROTHROMBOTIC EFFECTS
  - Abnormal LFTs

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Monoclonal antibodies 01:26:46

Anti SARS – CoV-2 monoclonal antibodies

- Target – Receptor binding domain of the spike glycoprotein
- Antibody cocktail – Casirivimab & imdevimab combination
  - Reduces chance of hospitalization by 70% in patients with mild-moderate disease
  - Reduces time to resolution of symptoms by 4 days

Received EUA in India on May 5

- Dose: 1200 mg (600mh of casirivimab & 600mg of imdevimab)

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- Intravenously (or) subcutaneously

Monoclonal antibodies (Casirivimab and Imdevimab)

- Aim of administration of anti-SARS-COV-2 monoclonal antibodies is to prevent disease progression in highest risk groups. So, it has to be administered early in the disease course before hypoxia develops
- It should NOT BE administered in
  1. Those who require oxygen therapy due to COVID-19; or
  2. Those who are on chronic oxygen therapy due to an underlying non-COVID-19-related comorbidity and, because of COVID-19, require an increase in oxygen flow rate form baseline
  3. More than 10 days from symptoms onset

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High-risk individuals who will benefit from Monoclonal antibody cocktail

- Body mass index (BMI) ≥35
- Chronic kidney disease stage with eGFR <60ml/min especially in those on MHD
- Diabetes mellitus (HBA1C>10) (or) diabetes with end organ damage
- Chronic liver disease
- Immunocompromising conditions
- Currently receiving immunosuppressive treatment

- Age ≥65years
- Cardiovascular disease
- Chronic respiratory diseases
- Malignancies with chance of survival
- Other indications as deemed fit by institutional medical board

2-deoxy-D glucose 01:31:08

- Modified glucose
- Acts by arresting viral replication
- Drugs Controller General of India (DCGI) on May 1 given EUA of 2DG on COVID-19 patients
- Powder form in a sachet. Dissolved in water & taken bd for at least a weak
- Causes faster recovery in COVID patients who are hospitalized
- Not in guidelines

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INFECTIVE ENDOCARDITIS

- Infection involving endocardial surface of heart (Predominantly valvular endocardium)
  ↓
  Can be native/prosthetic valve
- Rarely involves mural endocardium as well
- May develop in congenital heart defect like VSD
- Can occur due to infections involving indwelling cardiac devices.
  - Permanent pacemaker
  - Implantable cardioverter defibrillator
  - Ventricular assist device
- Prototype lesion in infective endocarditis – vegetation
- Vegetation is a mass composed of platelet, fibrin, few inflammatory cells, microorganisms
- Infection involving
  - Arteriovenous shunt
  - Arterio-arterial shunt (PDA)
  - Co-arctation of aorta

  } Infective endarteritis

Risk Factors 00:06:20

i. Rheumatic valvular heart disease

ii. Degenerative valvular heart disease

iii. Congenital heart disease

iv. Prosthetic valve

v. IV drug abusers

vi. DM

vii. Immunocompromised condition

viii. Patients with central venous catheter

ix. Patients on hemodialysis

x. Patient's on indwelling cardiac devices

Cardiac Lesions 00:09:37

- High risk cardiac lesions
  - Mitral valve prolapses with mitral regurgitation
  - Aortic stenosis
  - Aortic regurgitation
  - VSD
- All these are characterized by high pressure gradient
- Low risk cardiac lesions
  - MVP without MR
  - Mitral stenosis
  - ASD
- Hypertrophic cardiomyopathy can also predispose to infective endocarditis

Microbiology 00:12:55

- Big 3
  - Staphaureus
  - Streptococcus viridans
  - Enterococci
- Either can involve native valve (or) prosthetic valve

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- Native Valve Endocarditis
  - Community acquired → Strep. Viridans
  - Health care associated → Staphaureus

- Prosthetic valve endocarditis (PVE)
  - < 2 months → Early PVE → Nosocomial → Coagulase negative staph (CONS)
  - 2-12 months → Delayed nosocomial → CONS
  - >12 months → Late PVE → trep. Viridans

- IV drug abusers
  ↓
  - Staphaureus
  - Commonly causes right sided IE
  - Most common valve involved – Tricuspid
  - If left sided IE developed → Organism involved is enterococci > staph

- Cardiac implanted electronic devices
  ↓
  CONS

Organisms Causing Major Clinical Forms of Endocarditis									
	Percentage of cases								
	Native-Valve Endocarditis		Prosthetic-Valve Endocarditis at Indicated time of onset (months) After Valve Surgery			Endocarditis in Injection drugs users			
Organism(S)	Community Acquired (N=1718)	Health Care – Associated (N=1110)	< 2 (N=144)	2-12 (N=31)	>12 (N=194)	Right Sided (N=346)	Left sided (N = 204)	Total (N = 675)	CIED (N = 337)
Streptococci	40	13	1	9	31	5	15	12	2
Pneumococci	2	-	-	-	-	-	-	-	-
Enterococci	9	16	8	12	11	2	24	9	4
Staphylococcus aureus	28	52	22	12	18	77	23	57	36
Coagulase negative staphylococci	5	11	33	32	11	-	-	-	41
Fastidious gram – negative coccobacilli (HACEK group)	3	-	-	-		-	-	-	-
Gram – negative bacilli	1	1	13	3	6	5	13	7	6
Candida spp.	<1	1	8	12	1	-	12	4	2
Polymicrobial/ miscellaneous	3	3	3	6	5	8	10	7	2
Diphtheroids	-	<1	6	-	3	-	-	0.1	1
Culture-negative	9	3	5	6	8	3	3	3	6

- *Overall most common cause of infective endocarditis – staphaureus*

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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Challenges in Infective Endocarditis

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Erwan Salaun, MD,[d] Gosta B. Pettersson, MD, PHD,[f] Hans Joachim Schäfers, MD,[g] Bernard D. Prendergast, DM[h]

- Microbiology: Health care-associated organisms have increasingly defined the microbiology of contemporary IE. S aureus is now the most common causative organism and accounts for approximately 30% of cases (9,10). S aureus endocarditis is characterized by aggressive disease with increased risk of embolism, stroke, persistent bacteremia, and death (76). S aureus is also the most common cause of PVE,

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Microbiology of Infective Endocarditis						
	Native valve				Prosthetic valve	
		Health care – Associated IE (%)				
Organism	Community Acquired IE (%) (n=1201)	Nosocomial (n=370)	Non nosocomial (n=254)	Intravenous drug users with IE (%) (n=237)	Early IE (%) (n=140)	Late IE (%) (n = 390)
Staphylococcus aureus	21	45	42	68	34	19
Coagulase – negative staphylococci	6	12	15	3	28	20
Enterococcus species	10	14	16	5	10	13
Viridans group streptococci	26	10	6	10	1	11
Streptococcus gallolyticus	10	3	3	1	1	7
HACEK	3	0	0	0	0	2
Fungi	0	2	2	1	6	3
Other	13	7	10	7	6	15
Negative blood culture	11	7	6	5	14	10

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- Early PVE → staph aureus
- Late PVE → Cons
- In patients with prosthetic valves (see chapter 71), early prosthetic valve endocarditis has been defined as occurring as early as 60 days or less up to 1 year after surgery. S. aureus also is the leading pathogen in early prosthetic valve endocarditis (PVE), accounting for approximately 35% of cases, of which approximately one fourth are MRSA, followed closely coagulase – negative staphylococci. Streptococcal early PVE is unusual. Late PVE is caused less often by staphylococci, which nevertheless are still the most common infecting organism, and a higher occurrence of infections with both VGS and streptococcus gallolyticus (formerly S. bovis) has been documented. As with community – acquired native valve IE, enterococcal infections account for approximately 10% of cases of both early and late PVE.

Pathogenesis 00:33:17

- Prototype lesion in infective endocarditis – vegetation
- Vegetation is a mass composed of platelet, fibrin, few inflammatory cells, microorganisms
- Endothelial injury will attract platelets and fibrin

↓

Plug of platelet + fibrin

(sterile)

↓

Nonbacterial thrombotic endocarditis (NBTE)

- In certain hypercoagulable states like certain malignancies

  ↓

  Marantic endocarditis
- Vegetations were initially sterile → Nidus formation

  ↓

  Infective vegetation

  ↓

  Can embolize

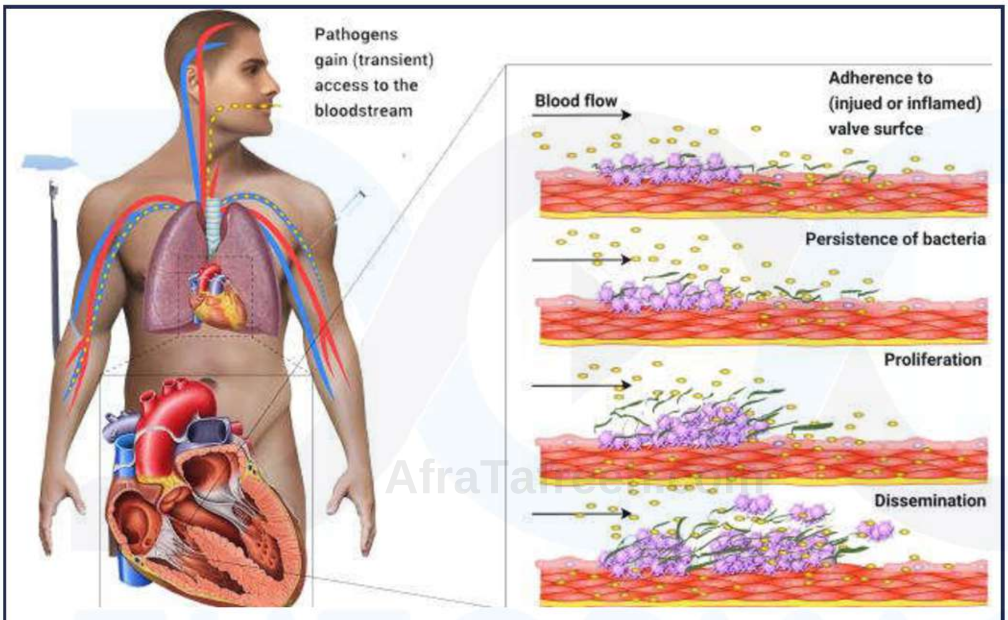

Fig: 1

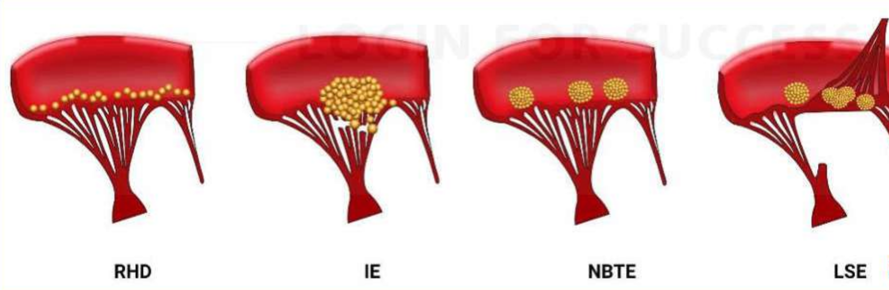

Fig: 2

- RHD – Small, warty vegetation occur along the lines of closure.
- IE – Large friable vegetations over superior surface of leaflet >> inferior

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- NBTE – small bland vegetations occur along lines of closure
- LSE – Small to moderate vegetations either superior or inferior surface of valve leaflet
- Vegetations of IE may cause chordae tendineae rupture

ICE – PCS Data

- Native valve endocarditis – 72%
- Prosthetic valve endocarditis – 21%
- Indwelling cardiac devices – 7%
- Mitral valve – 41%
- Aortic valve – 38%
- Tricuspid – 12%
- Infection prone state: Valvular regurgitant lesions >> stenotic lesions
- Incidence of IE is directly related to the impact of pressure on the closed valve, with shear stress disruption of the valvular endothelium in the vicinity of the egressing regurgitant jet.
- Venturi effect → Circulating organisms are deposited within the high velocity, lowered – pressure eddy zones of the regurgitant orifice of the receiving chamber.
- Leads to the typical localization of vegetations on the upstream aspect of the infected valve

Impact on heart

- Valvular vegetation
- Abscess
- Per-annular extension of infection
- Myopericarditis

IE in structurally normal valve

- Advanced age
- Renal failure requiring hemodialysis
- Infection by staph aureus or enterococci

Clinical Presentation 00:51:53

- Acute – days – 6 weeks → staphaureaus (common)
  Enterococci
- Subacute – 6 weeks – 3 months → most common, strep. Viridans
  Enterococci
  Staph
- Chronic/Indolent > 3 months → rare, bartonella
  T. whipplei
  C. burnetti

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Clinical and laboratory features of infective endocarditis

Feature	Frequency, %
Fever	80-90
Chills and sweats	40-75
Anorexia, weight loss, malaise	25 – 50
Myalgias, arthralgia	15-30
Back pain	7-15
Heart murmur	80-85
New/ worsened regurgitant murmur	20-50
Arterial emboli	20-50
Splenomegaly	15-50
Clubbing	10-20
Neurologic manifestations	20-40
Peripheral manifestations (Osler's nodes, subungual hemorrhages, Janeway lesions, Roth's spots)	2-15
Petechiae	10-40

- Most common – fever
- May develop mycotic aneurysm → focal dilatation

↓

Septic emboli

- Clubbing – feature of SABE
- Neurologic manifestation

- Stroke
- Brain abscess
- Meningitis

- Virulence of the infecting organism and persistence of bacteremia
- Extent of local tissue destruction of the involved valve and hemodynamic sequelae
- Perivalvular extension of infection
- Consequences of circulating immune complexes and systemic immunopathologic factors
- Septic embolization to any organ in the systemic arterial circulation or to the lungs.
- Septic embolization to lungs
  - Lung abscess
  - Empyema
  - Mycotic aneurysm
  - RHF
- Endocarditis caused by s. aureus
- Mobile vegetations >10 mm in diameter
- Infection involving the mitral valve, especially the anterior leaflet
  - Predisposing factors for septic embolization

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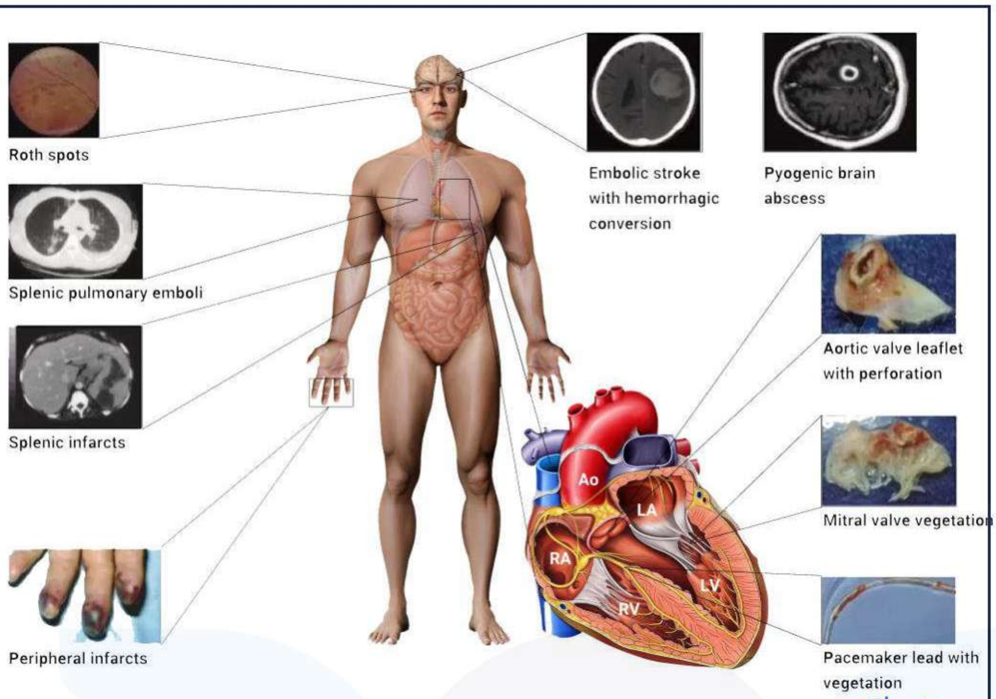

Fig: 3

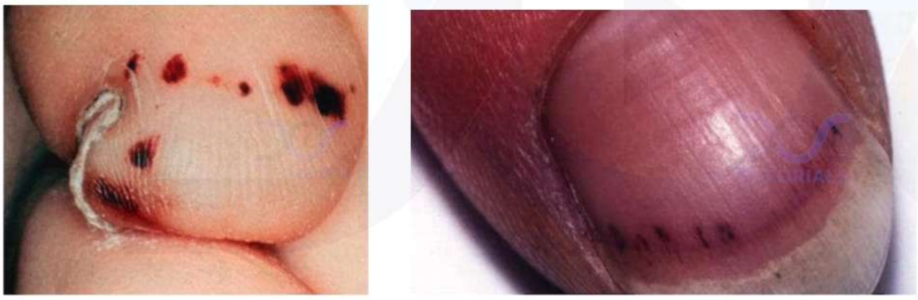
Fig: 4

- Splinter hemorrhages

↓

Linear/flame shaped hemorrhages

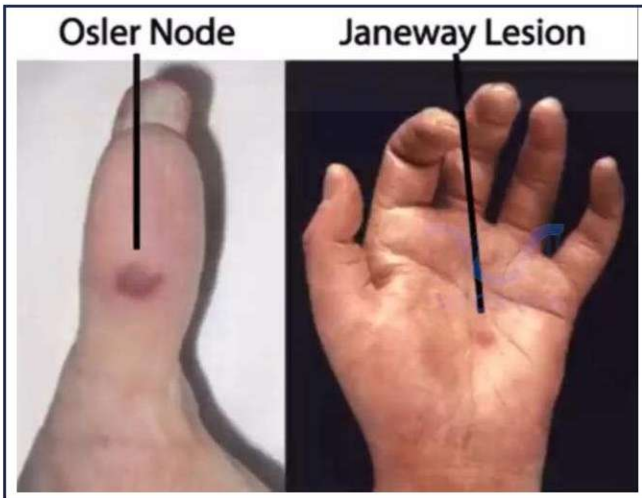

Fig: 5

- Janeway lesion
  - Result of septic embolization
  - Painless erythematous macular rash
  - Common in palms & soles
- Oster nodes
  - Painfull, tender lesions
  - Immunologic phenomenon
  - Common in pulp of finger

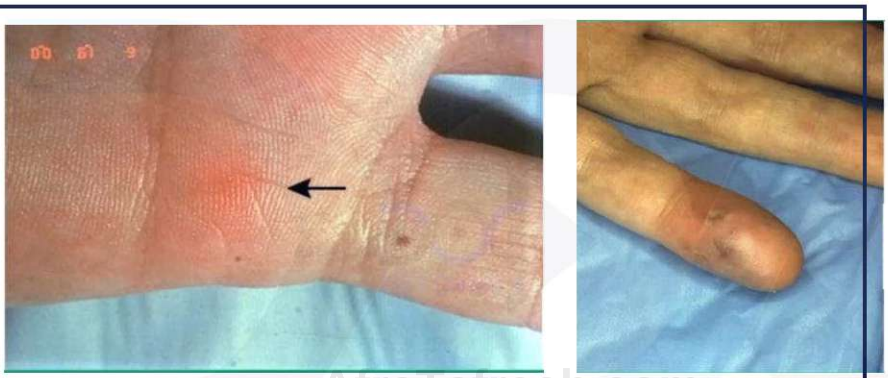

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Fig: 5

Fig: 6

- Janeway lesions

  Digital infarcts

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Fig: 7

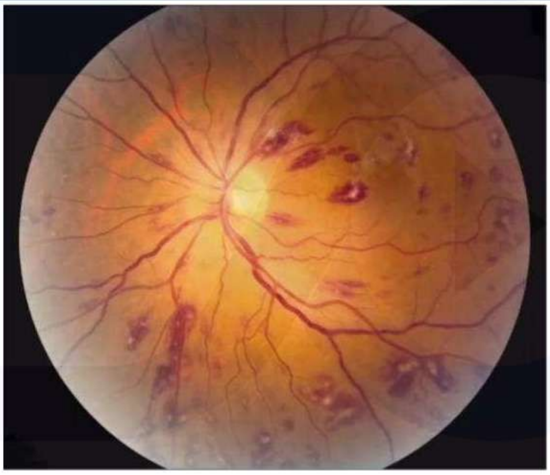

Fig: 8

- Roth spots

  ↓

  - Immunologic phenomenon
  - Hemorrhages with pale centres
  - Seen in SLE

    Leukemia

    Severe anemia

- Cardiac manifestations
  - Heart murmurs
  - Cardiac failure
  - Peri-vascular abscess

- Myocardial infarction
- Peri-vascular abscess may involve aortic valve

↓

May cause heart block

Investigations 01:14:54

Laboratory manifestations	
Anemia	70-90
Leukocytosis	20-30
Microscopic hematuria	30-50
Elevated erythrocyte sedimentation rate	60-90
Elevated C-reactive protein level	>90
Rheumatoid factor	50
Circulating immune complexes	65-100
Decreased serum complement	5-40

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Diagnosis 01:16:14

- 1994 – Duke criteria
- 2000 – Modified Duke Criteria
- Modified duke criteria is based on
  - Clinical features → Minor criteria
  - Microbiological evidence ┐ Major criteria
  - Echocardiography ┘

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The modified duke criteria for the clinical diagnosis of infective endocarditis

- Major criteria

1. Positive blood culture

- Typical microorganism for infective endocarditis from two separate blood cultures

  Viridans streptococci, Streptococcus gallolyticus, HACEK group Organisms, Staphylococcus aureus, or Community – acquired enterococci in the absence of a primary focus,

Or

- Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from:

  Blood cultures drawn > 12 h apart; or

  All of 3 or a majority of ≥ 4 separate blood cultures, with first and last drawn at least 1h apart

Or

- Single positive blood culture for Coxiella burnetiid or phase I IgG antibody titer of >1:800

2. Evidence of endocardial involvement

   Positive echocardiogram

Oscillating intracardiac mass on valve or supporting structure or in the path of regurgitant jets or in implanted material, in the absence of an alternative anatomic explanation, or

Abscess, or

New partial dehiscence of prosthetic valve,

Or

New valvular regurgitation (increase or change in preexisting murmur not sufficient)

- Minor criteria
  1. Predisposition: predisposing heart conditions or injection drug use
  2. Fever $\geq$ 38.0° C ($\geq$ 100.4° F)
  3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
  4. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor
  5. Microbiologic evidence: positive blood culture but not meeting major criterion, as noted previously, or serologic evidence of active infection with an organism consistent with infective endocarditis

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Major criteria

1. Positive blood culture
2. Echocardiographic evidence

1. Positive blood culture

Typical microorganism for infective endocarditis from two separate blood cultures

Viridans streptococci, streptococcus gallolyticus, HACEK group

Organisms, Staphylococcus aureus, or Community – acquired enterococci in the absence of a primary focus

OR

Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from:

Blood cultures drawn >12 h apart; or

All of 3 or a majority of ≥ 4 separate blood cultures, with first and last drawn at least 1 h apart

Or

Single positive blood culture for Coxiella burnetiid or phase I IgG antibody titer of >1:800

- 3 blood culture sets taken
- Each consists of 2 bottles → aerobic, anerobic

- Cultures are taken at 3 different sites over a period of 24 hours with minimum gap of 2 hours between each set.

2.Evidence of endocardial involvement

Positive echocardiogram

Oscillating intracardiac mass on valve or supporting structures or in the path of regurgitant jets or in implanted material, in the absence of an alternative anatomic explanation, or

Abscess, or

New partial dehiscence of prosthetic valve,

Or

New valvular regurgitation (increase or change in preexisting murmur not sufficient)

- Importance of echo – Vegetations
  Complication
  Cardiac function
- TTE (Transthoracic Echo) would be sufficient

Indications for transesophageal echo

- Prosthetic valve endocarditis
- CIED endocarditis
- Smaller vegetations (<2mm)
- Myocardial abscess
- Valve perforations
- Intracardiac fistulae

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Minor criteria

i. Predisposition: predisposing heart conditions or injection drug use

ii. Fever ≥ 38.0° C (≥ 100.4°F)

iii. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions

iv. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor

v. Microbiologic evidence: positive blood culture but not meeting major criterion, as noted previously, or serologic evidence of active infection with an organism consistent with infective endocarditis

- Organisms difficult to culture
  - Bartonella
  - Brucella
  - Legionella
  - C. psittaci
  - Coxiella
- Definite IE – Either 2 major criteria (or)
  1 major + 3 minor (or)
  5 minors
- Possible Infective Endocarditis –
  - 1 major criterion and 1 minor criterion, or
  - 3 minor criteria
- Rejected diagnosis of infective endocarditis

- Firm alternate diagnosis explaining evidence of suspected IE, or
- Resolution of IE syndrome with antibiotic therapy for ≤ 4 days, or
- No evidence of IE at surgery or autopsy, on antibiotic therapy for ≤ 4 days, or
- Does not meet criteria for possible IE.

- Modified duke criteria
  - Sensitivity – 80%
  - Specificity – 90%

Treatment 01:39:51

- Antibiotics
- Surgery

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Empiric antibiotic therapy

- Health care associated NVE
  Vancomycin plus gentamicin or cefepime
- NVE with a sub-acute presentation
  Vancomycin plus ceftriaxone
- Blood culture – pending PVE
  Vancomycin, gentamicin, and cefepime should be used if the prosthetic valve has been in place for ≤ 1 year empirical therapy for infected prosthetic valves in place for > 1 year is similar to that for culture – negative NVE.

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Antibiotic treatment for infective endocarditis caused by common organisms		
Organism(S)	Drug (dose, duration)	Comments
Pencillin – susceptible streptococci, S. gallolyticus (MIC ≤ 0.12 µg/ML)	• Pencillin G (2 -4 mU IV q4h for 4 weeks)	Can use ampicillin or amoxicillin (2 g IV q4h) if penicillin is unavailable.
	• Ceftriaxone (2 g/d IV as a single dose for 4 weeks)	Can use ceftriaxone in patients with non-immediate penicillin allergy.
	• Penicillin G (2-3 mU IV 14h) or ceftriaxone (2 g IV qd for 2 weeks Plus Gentamicin (3 mg/kg qd IV or IM, as a single dose or divided into equal doses q8h for 2 weeks)	Avoid 2 -week regimen when risk of aminoglycoside toxicity is increased and in prosthetic-valve or complicated endocarditis.
Relatively penicillin-resistant streptococci, S. gallolyticus (MIC > 0.12 µg/mL and <0.5 µg/mL)	• Penicillin G (4 mU IV 14h) or ceftriazone (2 g IV qd) for 4 weeks Plus Gentamicin (3 mg/kg qd IV or IM, as a single dose or divided into equal doses q8h for 2 weeks)	Can use ampicillin or amoxicillin (2 g IV q4h) if penicillin is unavailable. Penicillin alone at this dose for 6 weeks or with gentamicin during the initial 2 weeks is preferred for prosthetic-valve endocarditis caused by streptococci with penicillin MICs of ≤ 0.1 µg/mL
	• Vancomycin as noted above for 4 weeks	Use vancomycin if unable to tolerate penicillins. Ceftriaxone alone or with gentamicin can be used in patients with non-immediate β- lactam allergy.
Moderately penicillin – resistant streptococci (MIC, ≥ 0.5	• Penicillin G (4-5 mU IV 14h) or ceftriaxone (2 g IV qd) for 6 weeks Plus Gentamicin (3 mg/kg qd IV or Im as a single	Preferred for PVE caused by streptococci with penicillin MICs of >0.1 µg/mL.

μg/mL and <8 μg/mL) Granulicatella, Abiotrophia, or Gemelia spp.	dose or divided into equal doses q8g for 6 weeks)	
	• Vancomycin as noted above for 4 weeks	Regimen is preferred b7y some.

Enterococci

• Penicillin G (4-5 mU IV q4h) plus gentamicin (1mg/kg IV q8h), both for 4-6 weeks	Can treat NVE for 4 weeks if symptoms last <3 months. Treat PVE and NVE with >3 months of symptoms for 6 weeks. Can abbreviate gentamicin course in some patients (see text). Can use streptomycin (7.5mg/kg q12h) in lieu of gentamicin if there is not high-level resistance to streptomycin
• Ampicillin (2g IV q4h) plus gentamicin (1mg/kg IV q8h), both for 4-6 weeks	Can use amoxicillin in lieu of ampicillin (same dose)
• Vancomycin (15 mg/kg IV q12h) plus gentamicin (1 mg/kg IV q8h), both for 6 weeks	Use vancomycin plus gentamicin only for penicillin – allergic patients (preferable to desensitize to penicillin) and for isolates resistant t penicillin/ampicillin.
• Ampicillin (2 g IV q4h) plus ceftriaxone (2 g IV q12h) both for 6 weeks	Use for E.faecalis isolates without high-level resistance to gentamicin and streptomycin or for patients at high risk for aminoglycoside nephrotoxicity (creatinine clearance rate <50 mL/min: see text).

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Staphylococci (S. aureus and coagulase – negative)		
MSSA infecting native valves (no foreign devices)	• Nafcillin, oxacillin, or flucloxacillin (2 g IV q4h for 4-6 weeks)	Can use penicillin (4 mU q4h) if isolate is penicillin susceptible (i.e., does not produce β-lactamase); 6-week course preferred
	• Cefazolin (2 g IV q8h for 4-6 weeks)	Can use cefazolin regimen for patients with non-immediate penicillin allergy; 6-week course preferred
	• Vancomycin (15 mg/kg IV q12h for 4-6 weeks)	Only use vancomycin for patients with immediate (urticarial) of severe penicillin allergy; see text regarding addition of gentamicin, fusidic acid, or rifampin. A 6-week course is preferred.
MRSA infecting native valves (no foreign devices)	• Vancomycin (15 mg/kg IV 18-12h for 4-6 weeks)	No role for routine use of rifampin (see text). Consider high-dose daptomycin treatment (see text) for MRSA with vancomycin MIC >10 or persistent bacteremia during vancomycin therapy.
MSSA infecting prosthetic valves	• Nafcillin, oxacillin, or flucloxacillin (2 g IV q4h for 6-8 weeks) Plus Gentamicin (1mg/kg IM or IV q8h for 2 weeks) Plus • Rifampin (300 mg PO q8h for 6-8 weeks)	Use gentamicin during initial 2 weeks; determine susceptibility to gentamicin before initiating rifampin (see text); if patient is highly allergic to penicillin, use regimen for MRSA; if β-lactum allergy is of the minor non-immediate type, cefazolin can be substituted for oxacillin, nafcillin, or flucloxacillin.
MRSA infecting prosthetic valves	• Vancomycin (15 mg/kg IV q12h for 6-8 weeks) Plus	Use gentamicin during initial 2 weeks; determine gentamicin susceptibility before initiating rifampin (see text).

	Gentamicin (1 mg/kg IM or IV q8h for 2 weeks) Plus Rifampin (300 mg PO q8h for 6-8 weeks)	

Antibiotic Treatment for Infective Endocarditis Caused by Common Organisms		
Organism(S)	Drugs (dose, duration)	Comments
HACEK organisms		
	• Ceftriaxone (2 g/d IV as a single dose for 4 weeks)	Can use another third-generation cephalosporin at comparable dose.
	• Ampicillin/sulbactam (3 g IV q6h for 4 weeks)	If the isolate is susceptible, ciprofloxacin (400 mg IV q12h) can be used.
Coxiella burnetii		
	• Doxycycline (100mg PO q12h) plus hydroxychloroquine (200mg PO q8h), both for at least 18 (native valve) or 24 (prosthetic valve) months	Follow serology to monitor response during treatment (antiphase I IgG and IgA decreased 4-fold and IgM antiphase II negative) and thereafter for relapse.
Bartonella Spp		
	• Doxycycline (100 mg q12h PO) for 6 weeks Plus Gentamicin (1 mg/kg IV q8h for 2 weeks)	If doxycycline is not tolerated, use azithromycin (500 mg PO qd) some experts recommended that doxycycline be continued for 3-6 months unless all infection is resected surgically.

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Indications of surgery

Indications for cardiac surgical treatment in patients with endocarditis
Surgery required for optimal outcome
• Native-valve or prosthetic valve endocarditis – Moderate or severe congestive heart failure or shock due to valve dysfunction – Perivalvular extension of infection with abscess, fistula, or heart block – Persistent bacteremia without and extracardiac cause despite 7-10 days of optimal antimicrobial therapy. – Lack of effective antimicrobial therapy (e.g., fungal, Brucella, Multidrug-resistant gram-negative bacillary endocarditis) • Prosthetic-valve endocarditis – Partially dehisced unstable prosthetic valve
Surgery to be strongly considered for improved outcome
• Prosthetic – valve endocarditis – S. aureus infection with intracardiac complications – Relapse after optimal antimicrobial therapy • Native – valve endocarditis

- Large (>10 mm) hypermobile vegetation, particularly with prior systemic embolus and significant valve dysfunction
- Very large (>30mm) vegetation
- Persistent unexplained fever (≥ 10 days) in blood culture negative endocarditis
- Poorly responsive or relapsed endocarditis due to highly antibiotic – resistant enterococci or gram-negative bacilli

Prophylaxis 02:02:40

- Needed for high-risk cardiac lesion

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ACC-AHA focused update 2017

- Procedures for which infective endocarditis prophylaxis is recommended
  - Antibiotic prophylaxis is reasonable for all dental procedures that involve manipulation of gingival tissue, manipulation of the periapical region of teeth, or perforation of the oral mucosa for patients considered to be at highest risk (below)

High risk cardiac lesions

- High-risk cardiac lesions for which endocarditis prophylaxis is advised before dental procedures
  - Prosthetic heart valves

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- Prior endocarditis
- Unrepaired cyanotic congenital heart disease, including palliative shunts or conduits
- Completely repaired congenital heart defects during the 6 months after repair
- Incompletely repaired congenital heart disease with residual defects adjacent to prosthetic material
- Valvulopathy developing after cardiac transplantation

Antibiotic regimen for prophylaxis of endocarditis

A. Standard oral regimen

Amoxicillin: 2 g PO 1 h before procedure

B. Inability to take oral medication

Ampicillin: 2 g IV or IM within 1 h before procedure

C. Penicillin allergy

1. Clarithromycin or azithromycin: 500 mg PO 1 h before procedure
2. Cephalexin: 2g PO 1 h before procedure
3. Clindamycin: 600 mg PO 1 h before procedure

D. Penicillin allergy, inability to take oral medication

1. Cefazolin or ceftriaxone: 1 g IV or IM 30 min before procedure
2. Clindamycin: 600 mg IV or IM 1h before procedure.

BASIC TERMINOLOGIES

- pH: - Indication of amount of H^+ in body negative logarithm of H^+

  negative logarithm of H^+

  $pH = -\log (H^+) = \log 1/[H^+]$
- normal H^+ concentration in blood → 40 neq/L
- pH ∝ 1/ H^+
  - when you have H^+ increasing, pH decreases → acidosis
  - when you have H^+ decreasing, pH increases → alkalosis

H^+ Concentration (mEq/L) pH		
Extracellular Fluid		
• arterial blood	• 4.0×10^{-5}	• 7.40
• venous blood	• 4.5×10^{-5}	• 7.35
• interstitial fluid	• 4.5×10^{-5}	• 7.35
Intracellular fluid	1×10^{-3} to 4×10^{-5}	6.0-7.4
Urine	3×10^{-2} to 1×10^{-5}	4.5-8.0
Gastric HCL	160	0.8

- arterial blood pH range: - 7.35 – 7.45
- average pH of venous blood and interstitial fluid is less than arterial pH

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↓

- certain amounts of CO_2 is produced from the tissues to produce carbonic acid
- intracellular pH is lower than the plasma pH

Acid 00:13:33

- Molecules containing hydrogen atoms
- Release H^+ into the solution
- $HCl \rightarrow H^+ + Cl^-$
- H_2CO_3 (Carbonic acid) $\rightarrow H^+ \; HCO_3^-$

  $CO_2 + H_2O \rightleftarrows H_2CO_3 \rightleftarrows H^+ \; HCO_3^-$

  CO_2 - major source of H^+
- Strong acid

  HCl

  $H^+ \; H^+ \; H^+$

  $H^+ \; H^+ \; H^+$

  $H^+ \; H^+ \; H^+$
- Weak acid

  H_2CO_3

  $H^+ \; H^+$

Base 00:18:11

- Molecules that accept H^+

  $NaOH \rightarrow OH^- + H^+ \rightarrow H_2O$

  $HCO_3^- + H^+ \rightarrow H_2CO_3$

  Strong base – Na OH

  Weak base – HCO_3^-

- When you have pH change due to changes in Co_2 → respiratory process
- When you change in Hco_3^- – due to metabolic process
- Co_2 increase – Respiratory acidosis
- Co_2 decrease – Respiratory alkalosis
- Hco_3^- increase – Metabolic alkalosis
- Hco_3^- decrease – Metabolic acidosis

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BASICS OF ACID-BASE BALANCE

- Whenever there is a change in H^+ Concentration, our body will try to defend against the change in pH
- 3 defence systems

  1. Chemical acid-base buffers
  2. Respiratory system
  3. Renal system

  } Important to maintain arterial pH in the range of 7.35-7.45

Chemical acid-base buffers: 00:03:36

- Change in H^+ Concentration → first line of defence is contributed by Buffer system
- This response occurs within seconds
- These buffers Act by binding with acid and base
- Buffer: - any substance which can reversibly bind with H^+
- Buffer + H^+ ⇋ H Buffer

Law of mass action:

- The rate of reaction is proportional to the product of concentration of reactants
- Increased H^+ concentration → rightward shift of reaction
- Decreased H^+ concertation → leftward shift

Extracellular and Intracellular buffer

- Most common buffer in extracellular find → Bicarbonate buffer system

Bicarbonate buffer system

- $CO_2 + H_2O \leftrightharpoons H_2CO_3 \leftrightharpoons H^+ + HCO_3$

  ↓

  Carbonic anhydrase

- Addition of Hcl:

  Increased release of H^+ ions

  Binds with HCo_3^- → forms carbonic acid (H_2CO_3)

  ↓

  Formation $CO_2 + H_2O$

  ↓

  ↑↑ CO_2

  ↓

  Stimulate respiration

  ↓

  Eliminate CO_2 from respiratory System

  ↓

  CO_2 washout

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- Na OH added strong base)

↓

$NaOH^- + H_2CO_3 \rightarrow NaHCO_3 + H_2O$

$\uparrow OH \rightarrow \downarrow H_2CO_3$

↓

More H_2o combines with CO_2

↓

↓↓ Co2

↓

Inhibitory effect on the rate of respiration

↓

CO_2 retention

Phosphate buffer system

- It has an important role in buffering renal tubular, intracellular fluid
- Proteins are important intracellular buffers
- Hb is very important buffer in RBC
- $H^+ + Hb \leftrightharpoons HHb$

Respiratory regulation 00:18:51

- Co2 is formed continuously in the body

↓

Diffuses from the cells into blood and Interstitial Fuld

↓

lung alveoli

- Acts by Eliminating / retaining CO_2
- When there is an increase in ventilation → eliminates CO_2 From extracellular fluid → ↓ H^+ conc.
  - When there is decrease in ventilation → CO_2 Retention → ↑ H^+ conc.

↑ [H^+] → ↑ Alveolar ventilation
(−) ↑ ↓
↓ Pco_2

Respiratory system has Negative feedback on H^+ conc.

- Severe emphysema
  - Co_2 elimination defective
  - Co_2 build up
  - Respiratory Acidosis

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Renal system 00:25:29

- 3rd line of defence
- Takes hours to days
- Powerful system
  - Whenever kidney excretes acidic urine → it will reduce acid in extracellular fluid And vice versa

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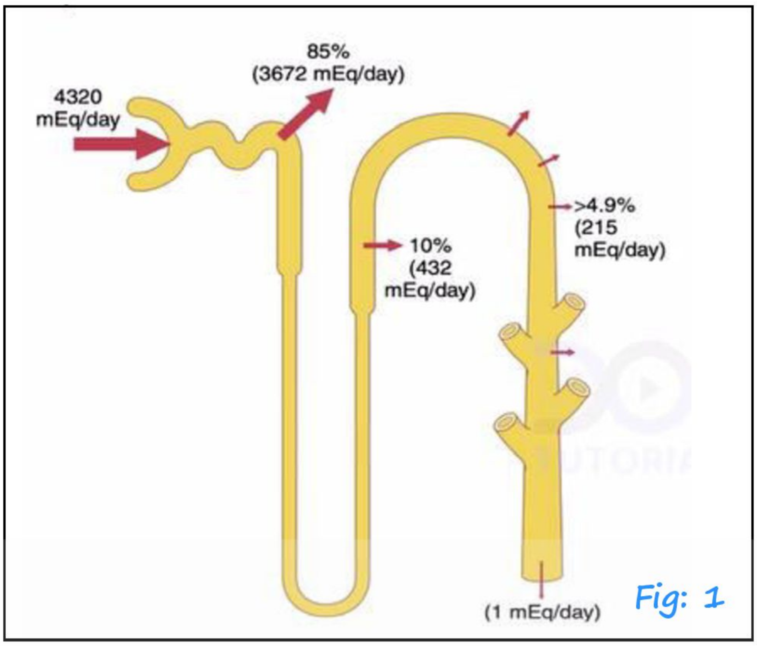

Fig: 1

Filtration & reabsorption of the Bicarbonate in the glomerulus

- Bicarbonate is filtered continuously along the glomerulus; it can be excreted in urine to remove the base.
- To remove H^+ from blood, H^+ is secreted to tubules from tubular epithelial cells
- In renal tubules, if more H^+ secretion > HCo_3^- filtered →net acid loss from ECF
- if more HCO_3^- filtered than H^+ secreted, there will be a net base loss from ECF
- kidney filters 4320meq of bicarbonate /Per day
- Under normal conditions, almost 4320meq of HCo_3^- Filtered is reabsorbed from tubules
  - In PCT → 80 – 85% Reabsorbed
  - Thick LOH → 10% Reabsorbed
  - CD → 5% Reabsorbed

3 Mechanism of regulation of H^+ conc.

- Secretion of H^+
- Reabsorption of filtered HCO_3^-
- Production of new HCO_3^-
  - In renal tubules, H^+ secretion and HCO_3^- reabsorption occur all parts except in thin descending and ascending limb of loop of Henle
  - The mechanism of H^+ secretion and HCo_3^- reabsorption is different in different parts of tubules

H+ secretion in early tubular segments

- PCT
- Thick ascending limb of LH
- Early distal tubule

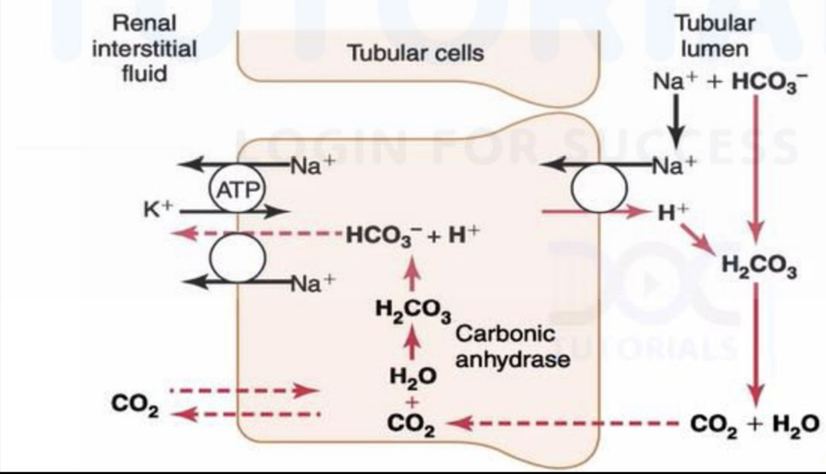

Fig: 2

- In early tubular segments, secretion of H^+ occurs via secondary active transport

↓

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Sodium – hydrogen counter transport

- At the basolateral membrane, energy produced from Na^+ K^+ ATPase is essential to pump the sodium- hydrogen counter transport
- This bicarbonate in the tubular lumen which is filtered across glomerulus, cannot directly reabsorbed
- $HCO_3^- + H^+ \rightarrow H_2CO_3 \rightarrow CO_2 + H_2O$
- CO_2 has the property of easily diffusing across the membrane
- CO_2 enters the cells and combines with H_2O and forms H_2CO_3
- H_2CO_3 dissociates to form $HCO_3^- + H^+$ and HCO_3^- is entering to the interstitial fluid via the basolateral membrane and taken by peritubular capillaries
- This brings urinary PH ~ 6.7
- In a normal individual, the rate of H^+ Secretion is 4400meq/day, there is a difference of 80
- This excess H^+ is to neutralise the non-volatile acids
- In metabolic alkalosis, there is an excess of bicarbonate in the urine, this bicarbonate cannot be reabsorbed, eventually excreted in urine and the body tries to correct the metabolic alkalosis by excreting alkaline urine.
- In metabolic acidosis, there is an excess of H^+ Compared to bicarbonate so as a result, complete

reabsorption of bicarbonate is in renal tubules and H^+ is excreted resulting in acidic urine

H^+ secretion in late distal tubule and collecting tubule:

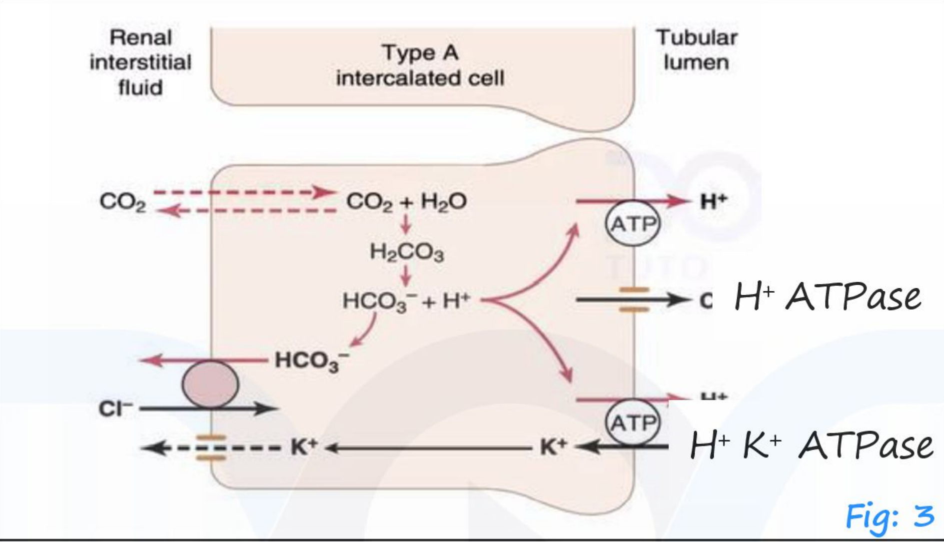

Fig: 3

- Primary active transport of H^+ occurs through certain specialised type of cells referred as Type A intercalated cells
- Type A intercalated cells have either H^+ ATPase or H^+ K^+ ATPase
- Through luminal side, there is active secretion of H^+ into tubular lumen
- In the cell, CO_2 reacts with H2O to form H_2CO_3. This H_2CO_3 dissociates into bicarbonate (HCO_3^-) and H^+ and this H^+ secreted into the tubular lumen either with help of H^+ ATPase or H^+K^+ ATPase
- For each H^+ Secreted into the tubular lumen, one bicarbonate goes into interstitial fluid and from there, it reaches the blood

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- This brings pH of the urine to 4.5 (acidification of urine)
- The amount of acidification is only 3-4 folds in proximal tubules where as in distal tubule, the amount of acidification is about 900 times
- H^+ secreted>>$HCO3^-$ filtered, only a small part of H^+ is excreted in the ionic form as H^+
- Majority of excess H^+ excreted in Combination with these tubular fluid buffers
  - Phosphate buffer
  - Ammonia buffer
  - Citrate buffer
  - Urate buffer

  Results in generation of new $HCO3^-$
- This process replenishes the $HCO3^-$ which lost from ECF during acidification of urine

Phosphate buffer

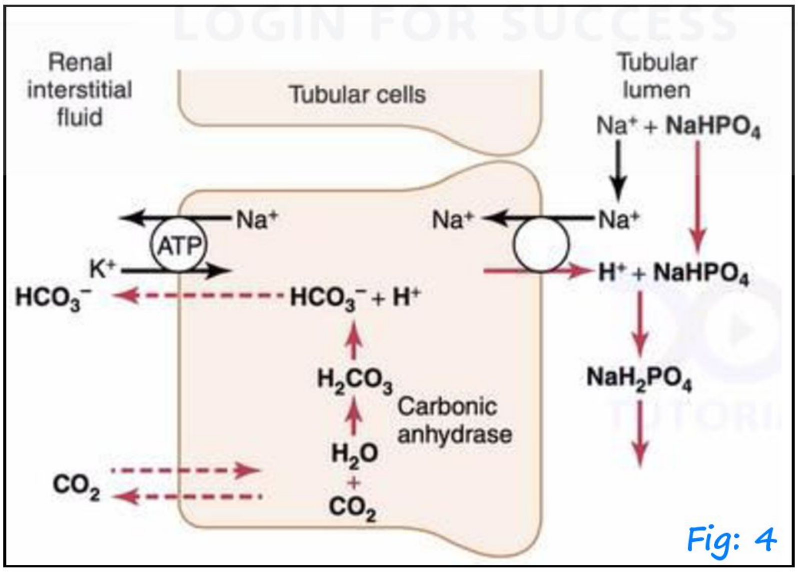

Fig: 4

- New bicarbonate is added to blood
- H^+ combines with phosphate buffer and excreted as NaH_2PO_4 (sodium salt)
- New bicarbonate which is generated in the cells enters into the interstitium through basolateral membrane then to the blood

Ammonia buffer system In proximal tubular cells:

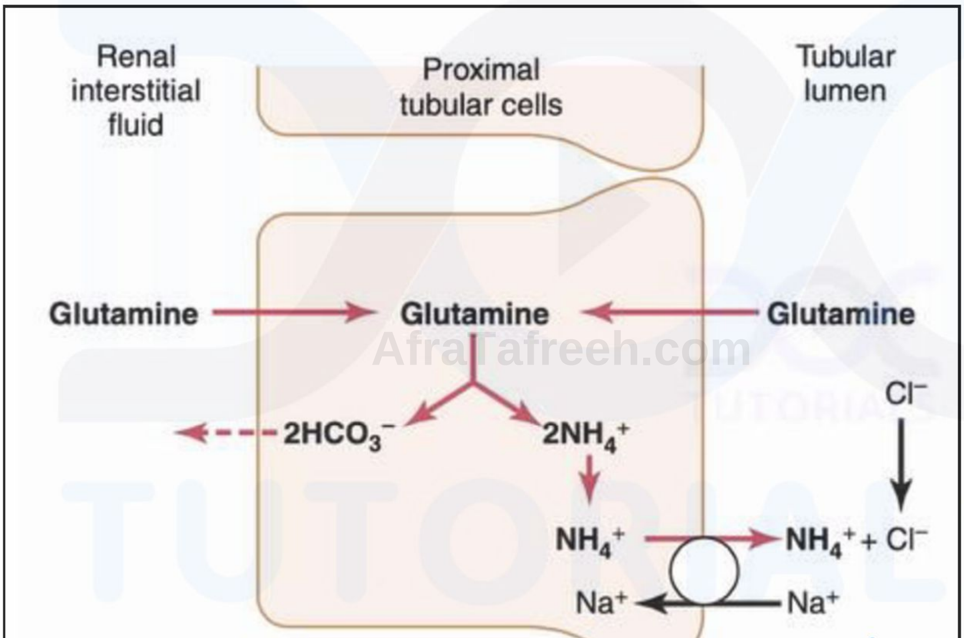

Fig: 5

- Consists of NH_3 (ammonia) and NH_4^+ (ammonium ion)
- glutamine is produced by Amino acid metabolism, reaches the tubular cells
- glutamine metabolizes to form 2 ammonium ions and 2 bicarbonate ions
- Ammonium secreted into tubular lumen by counter transport with Na+

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- New bicarbonate is transported to peritubular capillaries

In collecting tubules:

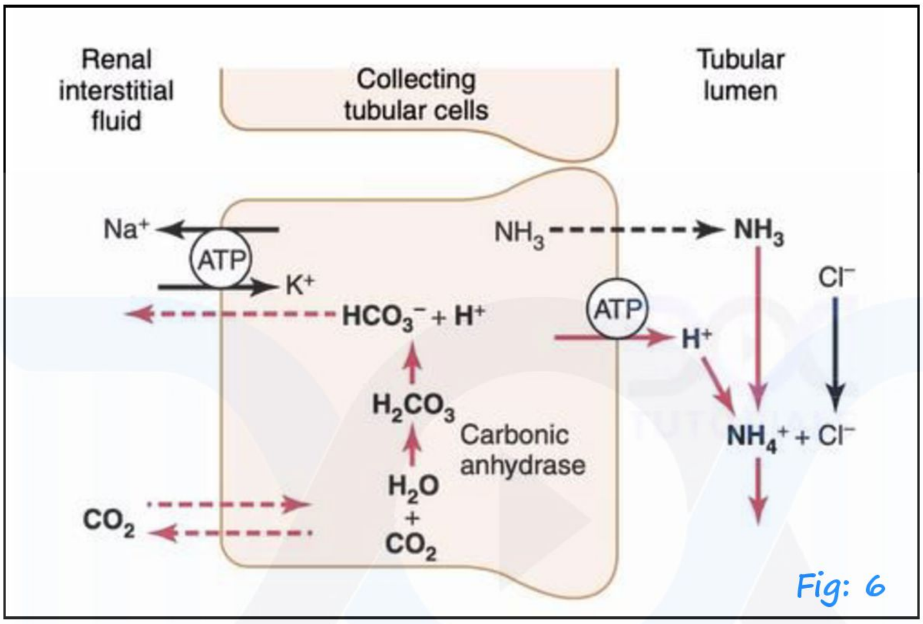

Fig: 6

- The H^+ is actively secreted in the tubular lumen and it combines with ammonia to produce ammonium ion
- Collecting ducts are impermeable to ammonium ion so excreted in urine
- For each NH_4^+ that is secreted, new bicarbonate is formed

Henderson Hasselbach Equation

- pH is inversely proportional to CO_2
- pH is directly proportional to HCO_3^-
- $pH = 6.1 + \log HCO_3^- / Pa\ CO_2 \times 0.003$

- Normal values:
- pH = 7.35-7.45 (7.4)
- HCO_3 = 22-26meq (24)
- CO_2 = 35-40mmHg (40)

Relationship between plasma pH and K+ conc.

- Acidosis → k+ moves into plasma

  ↓

  Hyperkalaemia

- Alkalosis → hypokalaemia

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TYPES OF ACID BASE DISORDER

Types of Acid Base disorder

- Simple
- Mixed

Simple acid base disorder 00:01:40

- Whenever these is primary acid base disturbance, body will have its own mechanism to normal pH

  ↓

  Compensatory response
- If the primary problem is respiratory ($PaCo_2$) then compensatory would be metabolic (HCo_3^-)
- Similarly, if the 1° problem is metabolic (HCo_3) compensatory would be respiratory
- If there is no definite compensation, pH cannot be maintained in the physiological range
- Compensation is a predictable physiology consequence of the 1° disturbances
- Compensation → brings pH towards normal, but not to the normal value
- Exception is chronic respiratory alkalosis → may return pH to normal value

1° respiratory acidosis

↓

- Co_2 retention
- pH ↓

] Main compensation is metabolic – retain HCO_3^-

- In 1° respiratory acidosis, the compensatory mechanism is metabolic alkalosis

1° respiratory alkalosis

↓

- Co_2 wash out
- pH ↑
- Compensation via HCo_3 → lose HCo_3^-

↓

Metabolic acidosis

Primary metabolic acidosis

- ↓ HCo_3^-
- ↓ pH
- Compensation via Co_2 wash out

↓

Respiratory alkalosis

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Primary metabolic alkalosis

- HCo_3^- ↑
- pH ↑
- Compensation → Tetain Co_2

↓

Respiratory acidosis

- Patient with DKA → there is endogenous acid production, ↓ HCo_3^-, ↓ pH
  - Stimulate medullary chemo receptors
  - ↑ rentilation
  - pH returns towards normal

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Summarizing primary change and compensation

- Metabolic acidosis
  pH ↓ HCO_3^- ↓ $PaCO_2$ ↓
- Metabolic alkalosis
  pH ↑ HCO_3^- ↑ $PaCO_2$ ↑
- Respiratory acidosis
  pH ↓ $PaCO_2$ ↑ HCO_3^- ↑
- Respiratory alkalosis
  pH ↑ $PaCO_2$ ↓ HCO_3^- ↓

Rules of compensation 00:17:21

- Complete compensation doesn't happen
- Respiratory compensation is faster than metabolic compensation
- Compensation response depends on
  - Proper functioning of compensatory organ system
  - Severity of acid base disturbance
- In a simple acid base disorder
  - Primary change and compensation move together
- In a primary respiratory disorder,
  - Change in pH in relation to CO_2 and HCO_3^- will be in opposite direction.
- In primary metabolic disorder, change in pH in relation to CO_2 and HCO_3^- will be in same direction

- **Primary process**
  - pH → 7.5 ↑
    CO_2 → 26 ↓
    HCO_3^- → 20 ↓

  ] Respiratory Alkalosis

- pH → 7.3 ↓
  CO_2 → 24 ↓
  HCO_3^- → 12 ↓

  — Metabolic Acidosis

Calculation of compensation

- If the primary respiratory acidosis → these will be renal compensation to retain bicarbonate
- In acute respiratory acidosis, for every 10mm increase in CO_2, bicarbonate increases by 1 meq
- In chronic respiratory acidosis, for every 10mm litres increase in CO_2, HCO_3^- increases by 4 meq

Respiratory alkalosis

- Renal compensation occurs by excreting HCO_3^-
- In acute respiratory alkalosis, for every 10mm litres ↓ CO_2, HCO_3^- decreases by 2 meq
- In chronic respiratory alkalosis, for every 10 mmHg decrease CO_2, HCO_3^- decreases by 4 meq

Myasthenia Gravis

- Chronic neuro muscular junction disorder
- pH: - 7.32 ↓
  $PaCO_2$: - 60mm ↑
  HCO_3^-: - 32 ↑

  — Respiratory acidosis

↓

20 mm Hs ↑ CO_2 →

For 10 mm Hs → 4 meq ↑ HCO_3^-

20 mm Hs → 8 meq

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$$24 + 8 = 32$$

↓

Compensated

- Chronic respiratory acidosis with compensatory metabolic alkalosis
- Chronic compensated respiratory acidosis

Metabolic Acidosis

- Respiratory compensation → winter's formula
  - Expected $CO_2 = (1.5 \times HCO_3^-) + 8 \pm 2$

  pH – 7.3 ↓ → Metabolic acidosis
  CO_2 – 24 ↓ Adequately
  HCO_3^- – 12 ↓ compensated

  - Expected $CO_2 = (1.5 \times 12) + 8 \pm 2$

$$= 18 + 8 \pm 2$$
$$= 18 \pm 2$$
$$= 24 - 28$$

Metabolic Alkalosis

- Exp $CO_2 = HCO_3^- + 15$

Mixed Acid base disorder

- In an individual, these are independently co-existing acid base disorders
- It is not merely a compensatory response
- In mixed acid base disorder, these is inappropriate compensation

- A patient with COPD & T_2DM → DKA

↓ Point has insufficient Respiratory reserve

↓ Respiratory acidosis on Metabolic acidosis

↓ Severe acidemia

↓ metabolic acidosis

- Patient of DKA → pneumonia

↓

Mixed acid base disorder

- Metabolic acidosis and metabolic alkalosis can be present in same person
- pH can be normal

Triple acid base disorder

- Alcoholic Ketoacidosis → metabolic acidosis

↓

Vomiting → metabolic alkalosis

Alcohol withdrawl – respiratory alkalosis

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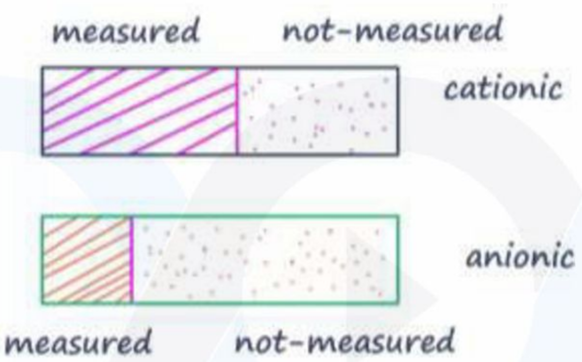
ANION GAP

- Serum anion gap
- Urine anion gap

Serum anion gap 00:01:23



- Cationic compartment consists of positively charged ions. Some of the ions in the cationic compartment are the ones which are routinely measured where as some of the cations are ones which cannot be routinely measured.
- The total number of cations should be equal to total number of anions obviously to maintain ______
- Anion gap is the gap between major measured cations (Na^+ and K^+) and major measured anions (Hco_3^- and Cl)
- Anion gap = $Na^+ - (Hco_3^- + cl^-)$
- Normal anion gap =
  - 8–12 meq/L (average: – 10 meq/L)
  - 6–12 meq/L

Un-measured anions contributing to this gap

- Anionic proteins (albumin and β globulins)
- Phosphate and sulfate
- AG
  - If there is reduction in albumin level 1g/dl (N- 4.5g/dl). AG will decrease by 2.5g/dl corrected anion gap = observed AG + 2.5 [4.5-measured albumin g/dl]
  - If there is addition of acid → there is lot of H^+, this H^+ will combine with bicarbonate → measured anion part shrinks and anion gap increases
  - If acid added is hydrochloric acid → though bicarbonate is lost, chloride will be added to anionic compartment, so decrease in serum bicarbonate is matched by an equal increase in serum chloride → Anion gap normal

    ↓↓
  - As chloride is increased, can be called as hyperchloremic metabolic acidosis
  - Whenever an H^+ is accompanied by anion other than chloride, like lactate → decrease in bicarbonate is balabnced by increase in concentration of the unmeasured anion

    ↓↓

    High anion gap metabolic acidosis (HAGMA)
- Simple HAGMA

  Increase 1 meq/ 1 AG → decrease 1 meq/ 1 Hco_3

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CAUSES OF HAGMA

- Lactic acidosis
- Ketoacidosis → DKA, AKA, starvation
- Toxins
  - Ethylene glycol
  - Methanol
  - Propylene glycol
  - Salicylates
- Renal failure

Lactic acidosis 00:02:32

Lactic acidosis

- End product of anaerobic metabolism of glucose
- Lactic acidosis occurs when there is imbalance between production and the use of lactic acid.
- Accumulation of serum lactate → metabolic acidosis
- 2 types
  - Type A
- Under perfusion of tissues or acute hypoxia
  - Type B
- Absence of overt hypoperfusion or hypoxia

Causes of Lactic Acidosis

Type A (Tissue under perfusion or hypoxia

- Cardiogenic shock
- Septic Shock
- Hemorrhagic shock
- Acute hypoxia
- Carbon monoxide poisoning
- Anemia

Type B (Absence of Hypotension and Hypoxia)

- Hereditary enzyme (Glucose 6-phosphatase
- Drugs or toxins
- Phenformin, Metformin
- Cyanide
- Salicylate, Ethylene glycol, Methanol
- Linezoid
- Propofol
- Nucleoside reverse transcriptase inhibitors: Stavudine, didanosine
- Clebuterol
- Isoniazid
- Thiamine deficiency
- Systemic disease
- Malignancy

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Treatment

- Correction of underlying disorder
- Restore tissue perfusion and oxygenation
- Role of alkali: - controversial

  $NaHCO_3$ → paradoxically depress cardiac function

  ↑ lactate → worsens acidosis
- Severe acidemia → alkali pH < 7.1

DKA 00:10:37

- Increase in fatty acid metabolism
- Accumulation of keto acids like acetoacetate or β hydroxy butyrate will increase anion gap and results in high anion gap.

Starvation KA 00:12:05

- Increased mobilization of FA

  ↓

  Ketoacids

Alcoholic KA 00:12:58

- Nausea, vomiting, abdominal pain
- ↓ insulin glucagon ratio
- Associated with mixed acid base disorders
- R_p: - IV glucose and insulin administration
- May have associated hypophosphatemia, hypokalemia, hypomagnesemia

- Toxins
  - Osmolal gap
  - Toxin induced metabolic acidosis

Plasma osmolality

- Concentrates of solutes in a given weight of water (275-295 mosm/kg)
- Contributed by Na, urea glucose

  $$\text{Osmolality} = 2[Na+] + \frac{BUN}{2.8} + \frac{Glucose}{18}\ (mg/dl) \rightarrow$$

  Calculated osmolality
- Measured osmolality by osmometry

  Osmolal gap = measured osmolality – calculated osmolality
- Normally it is < 10 mosm/kg
- If difference exceeds > 10 mosm/kg

  ↓

  2 possibilities
  - Serum Na+ spuriously low

    ↓

    Hyperlipidemia
    Hyperproteinemia } Pseudo hyponatremia
  - Presence of other osmolytes in plasma

    ↓

    Ethylene glycol
    Ethanol
    Mannitol
    Radio contrast

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Ethylene glycol:

- Commonly used as antifreeze

  ↓

- Can lead to HAGMA
- High anion gap
- High osmolol gap
- Oxalate crystals in urine
- Rx: - Supportive
- Rx: - Saline or osmotic diuresis Thiamine, pyridoxine supplements

  – Fomipezole (agent of choice)

- Competitive inhibitor of alcohol dehydrogenase if not available – iv ethanol

  – Hemodialysis (pH < 7.3)

  – Bicarbonate therapy

Salicylates

- Most common disturbance associated with salicylate toxicity → respiratory alkalosis
- Can cause HAGMA → because of uncoupling of oxidative phosphorylation
- Rx: - Vigorous gastric lavage with isotonic saline activated charcoal via NG tube

  IV Na HCO_3 – HAGMA

  Hemodialysis in severe poisoning

Renal failure 00:28:59

- Early stages of CKD – Hyperchloremic acidosis
- Advanced CKD – HAGMA
- Decreased ammonia production and excretion
- Rx:
  - Oral alkali
  - Na HCO_3 tablets
  - Shohl's solution – sodium citrate

Citrate → bicarbonate

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NAGMA

- Normal anion gap MA
- Non anion gap MA
- Bicarbonate is effectively replaced by u-hence the anion gap is normal.

Etiology

- Occurs because of renal causes and extra-renal causes
- Mostly due to diarrhea → loss of bicarbonate from GIT, it eventually results in metabolic acidosis
- Renal acidification defects
- Based on renal tubular response → able to comment on renal or extrarenal cause
- If you have an appropriate tubular response, it means the renal tubules are intact and it can be extrarenal or gastrointestinal origin
- If the renal tubular response is inappropriate → renal origin
- In metabolic acidosis, utilization of ammonia buffer system → Ammonia excretion increase

↓

New Hco_3- generation

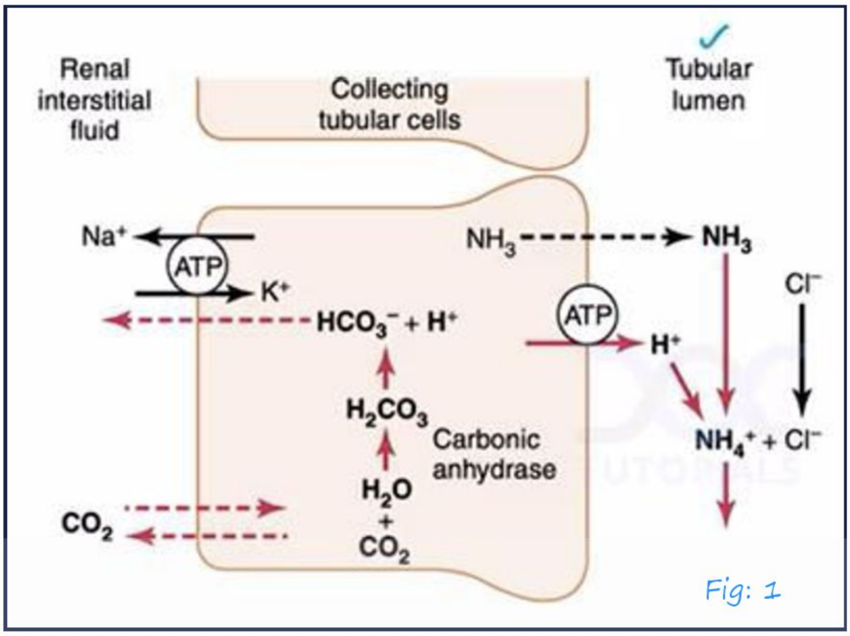

Fig: 1

- If extra-renal cause → appropriate renal response

  ↓

  High urinary ammonium excretion

- If it is renal cause → low urinary ammonium excretion

  Indirect estimate of urinary ammonium excretion

  ↓

  - Urine anion gap
  - Urine osmolal gap

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Urine anion gap 00:11:48

UAG = $[U_{Na} + U_{K^+} - U_a]$

Meq 11 (or) mm10/1

- Normal value of urinary anion gap: - 30-50mm01/1

  In Diarrhoea → loss of Na^+, K^+, HCo_3^-

  ↓

  Decrease renal excretion of Na^+ & K^+

  NH_4^+ → unmeasured cation

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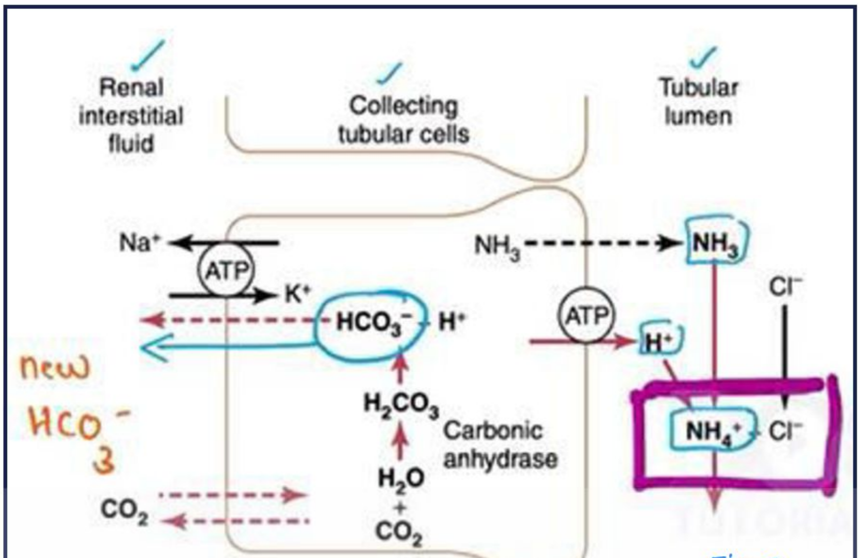

Fig: 2

→ UAG progressively negative

Negative UAG indicates extra-renal origin of NAGMA

- In renal tubular acidosis → Tubular dysfunction

↓

Excretion of ammonium ↓

↓

Unmeasured cation is decreasing

→ Positive UAG

- Positive UAG indicates either → normal ammonium excretion
  ↘ Low ammonium excretion

Urine osmolal gap 00:22:17

- Difference between measured & calculated urine osmolality

$$\text{Calculated (mosml / kg)} = 2(Na^+ + K^+) + \frac{\text{urea nitrogen mg/dL}}{2.8} + \frac{\text{Glucose in mg/dl}}{18}$$

Urine osmolal gap: – 10–100 mosml/kg

NH_4^+ – generally the only other major urinary solute that can contribute to the urine osmolality

- UOG >100 mosol/kg → increased excretion of NH_4^+ salts
- Urine pH
  - In Diarrhea, loss of HCO_3^- → Metabolic acidosis

↓

Low urinary pH

Sometimes pH ≥ 6

When you have chronic metabolic acidosis, there will be ↑ NH_4 synthesis & excretion

↓

increase urinary pH

- Urinary pH → does not differentiate renal vs extrarenal

Urinary diversion procedures associated with NAGMA

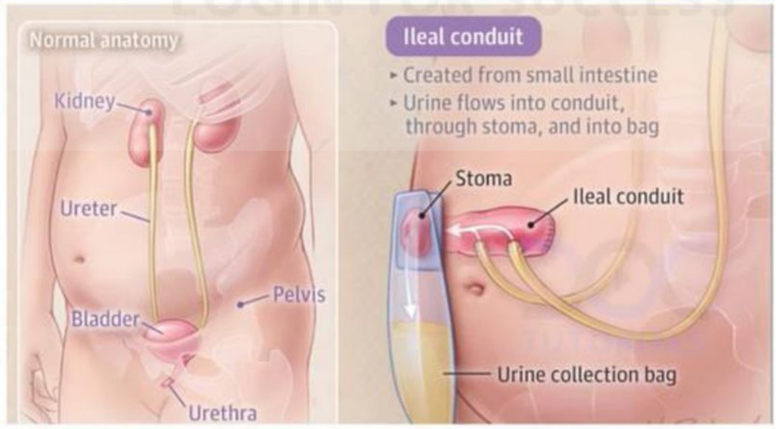

Fig: 3

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- Commonly used are Ileum, colon
- They will consist of Cl^- / Hco_3 exchangers
- There is exchange of HCo_3^- with Cl^-
- Results in hyperchroremic NAG metabolic acidosis
- In uretero-sigmoidostomies → prolonged transectile of urine.

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RENAL TUBULAR ACIDOSIS (RTA)

- Group of disorders → metabolic acidosis due to defective renal tubular function
- They have relatively well preserved GFR
  Type II RTA → impaired GFR
- All types of RTA are characterized by NAGMA

Types of RTA 00:03:14

Proximal RTA (Type 2 RTA)

- ↓ HCO_3^- reabsorptive capacity
- Bicarbonate wasting in urine

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Classic distal RTA (Type 1 RTA)

- Impaired distal acidification

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Mixed (Type 3)

- Type 2+1
- Carbonic anhydrase II deficiency AR

Hyperkalemic form of distal RTA

- Type IV RTA

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Proximal RTA

- 80-90% filtered HCO_3^- in proximal tubule
- In proximal RTA, there is decreased capacity to reabsorb HCO_3^-
- The bicarbonate flows through the renal tubule and go flood the distal tubule
- When the capacity is exceeded → bicarbonate in urine → bicarbonate

  S. HCO_3^- decreased (15-18 meq/L) steady stare

  serum HCO_3^-

  ↓

  Filtered HCO_3^- decrease

  ↓

  Proximal tubule reabsorbs filtered HCO_3^-

  ↓

  DCT reabsorbs the remaining part

  – Distal nephron can acidify urine to $pH < 5.5$

  In steady state proximal RTA

  ↓

  Individual has chronic metabolic acidosis

  – Acid urine pH

  – Low fractional excsetion of HCO_3^-
- In case of proximal RTA, hypokalemia is present

  ↓

  When there is renal $NaHCO_3^-$ loss → leads to intravascular volume depletion

  ↓

  RAAS activation

- There is increased ↑ Distal Na^+ delivery
  ↓
  – Na^+ reabsorption
  – K^+ secretion
- Proximal RTA occurs in
  – Isolated HCO_3^- reabsorption defect
  – Mixed RTA
  – Generalized proximal tubular dysfunction (Fanconi Syndrome)
    1. Glucose
    2. Amino acids
    3. Phosphates
    4. Uric acid
    5. Citrate
- Fanconi syndrome → Inherited and acquired causes
- Adults with Fanconi syndrome – commonly associated with dysproteinemias
  ↓
  Commonly occurs in context with multiple myeloma
  In children, Fanconi's syndrome is caused by
  – Cystinosis
  – Wilson's disease
  – Hereditary Fructose intolerance
  – Lowe Syndrome
  – Metachromic leukodystrophy
- In proximal RTA, many of the patients have
  – Skeletal abnormalities
  – Osteomalacia → because of renal phosphate wasting

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- Deficiency in active form of vitamin D
- Not associated with Nephrolithiaris or Nephrocalcinosis

Drugs associated with type 2 RTA

- Acetazolamide
- Topiramate → associated c renal stones

Drugs associated with Fanconi

- Outdated tetracycline
- Ifosfamide
- Gentamicin
  - Hyperparathyroidism associated with Fanconi's Syndrome

Treatment of Type 2 RTA

- Most challenging
- If alkali is given
  ↓
  - ↑ Serum HCO_3^-
  - ↑ urinary bicarbonate loss
  - Worsening of hypokalemia (preventing by giving potassium citrate)
- When compared children with adults, children should be aggressively treated

Classic Distal RTA 00:27:42

- Impaired distal acidification
- Reduction in net H^+ secretion in distal nephron
- Prevents urinary acidification
- There is acid accumulation
- Metabolic acidosis stimulates reabsorption of bone matrix → release calcium alkali salts from bone

  ↓

  Results in osteopenia – adults

  Osteomalacia – children
- Urinary calcium excretion high

  There is acidosis induced bone mineral dissolution

  The luminal alkalinization in renal tubules will inhibit calcium reabsorption → This will further increase urinary Ca^{2+} excretion
- Classic distal RTA very well known for Nephrolithiaris and Nephrocalcinosis
- Can have patient having mild metabolic acidosis to very severe acidosis
- Serum HCO_3^- levels vary from 10-20
- Can have hypokalemia due to urinary k^+ loss
- Distal RTA can occur either
  - Primary
    - Idiopathic
    - Familial
  - Secondary
    - Systemic disease

      ↓

      Sjogren syndrome

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- Amphotericin B
- Hyperparathyroidism
- Vitamin D intoxication

Treatment of distal RTA

- Alkali therapy
- Potassium correction → corrected before acidosis or after acidosis

  $NaHCO_3$ will further lower serum k^+

  Hence a combination of sodium alkali and potassium alkali
- For chronic therapy → $NaHCO_3$ tablets

  Shohl's solution

  Sodium citrate

Hyperkalemic distal RTA 00:39:14

- Also referred to as generalized distal RTA
- There is generalized distal nephron dysfunction

  ↓

  Causes cortical and medullary CD
- This will result in impaired renal secretion of both H^+ & K

  – NAGMA

  \+

  – Hyperkalemia

- Most common associated with hyporeninemic hypoaldosteronism diabetic nephropathy

  ↓

  Destructive of JG apparatus because of vascular hyalinosis
- In type IV RTA → there can be mild – moderate impairment in renal function
- There is disproportionate hyperkalemia
- Conditions associated with type IV RTA
  - Obstructive nephropathy
  - CTID
  - Drugs:
    - NSAIDS
    - ACEI
    - ARBS
    - Spironolactone
    - Amiloride
    - Pentamidine
    - Trimethoprim
- HCO_3^- level: - 18-22
- K^+: - 5.5-6.5

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Treatment

- Hyperkalemia
- Metabolic acidosis
- Correction of hyperkalemia increases renal ammonia production

  ↓

  Improves distal acidification

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- ACEI / ARB → cardiovascular benefits and reno protector
- In aldosterone deficiency → fludrocortisone 0.1 mg/day
- Loop & thiazide diuretics → Increases K^+ + H^+ secretion in CD
- Alkali therapy → $NaHCO_3$ → watch out for volume overload & worsening of HTN

Tubular acidosis types			
Factor	Type 1	Type 2	Type 4
Serum K^+	Low	Low	High
Renal function	Normal or near normal	Normal or near normal	Stage 3,4 or 5 chronic kidney disease
Urine pH during acidosis	High	Low	Low or High
Serum HCO-3 (mmol/l)	10-20	16-18	16-22
Urine citrate	Low	High	Low
Fanconi syndrome	No	May be present	No

OVERVIEW OF CIRRHOSIS

Cirrhosis 00:00:30

- Pathogenic entity
- Diffuse hepatic fibrosis
- Distortion of normal hepatic parenchymal architecture

↓

Nodules

- Focal nodular hyperplasia

Etiologies 00:03:12

- Alcohol
- Chronic viral hepatitis
- NASH
- Metabolic: - Wilson's disease
  - Hemochromatosis
  - α_1-antitrypsin deficiency
- Cystic fibrosis
- Autoimmune hepatitis
- Cardiac cirrhosis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Cryptogenic cirrhosis
- Final common pathway for many chronic liver disease

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Pathogenesis 00:07:04

- Hepatic stellate cell (HSC) → located in normal liver in space of Disse
- Normal function of stellate cell sis to store vitamin A
- Fibro genic stimuli will activate the hepatic stellate cell

↓

Activation and transdifferentiating of HSC → myofibroblast

- myofibroblast secretes extracellular matrix components

↓

Fibronectin -1, Type I collagen

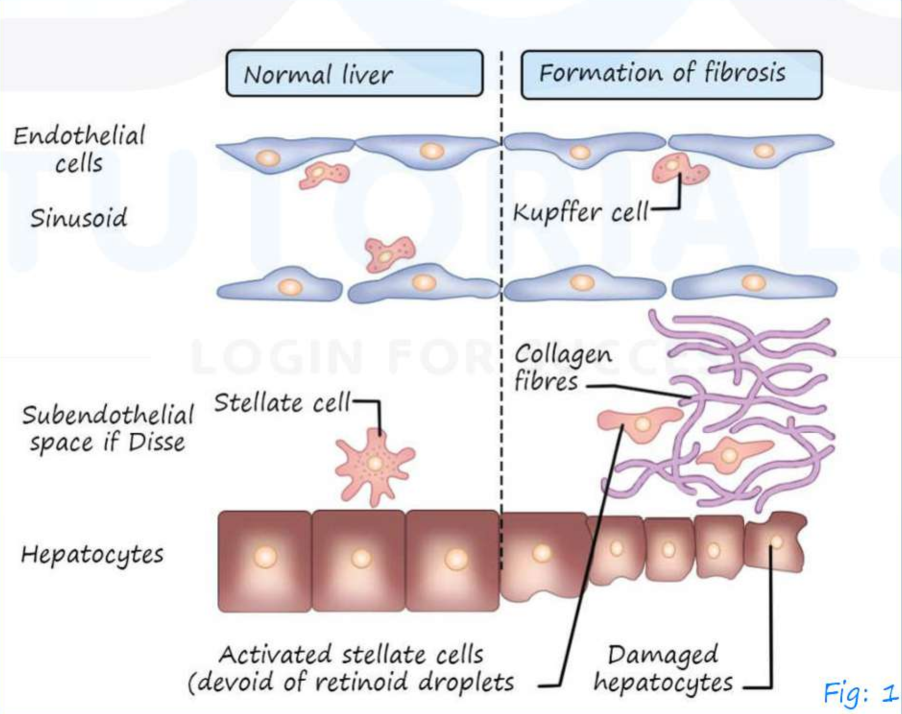

Fig: 1

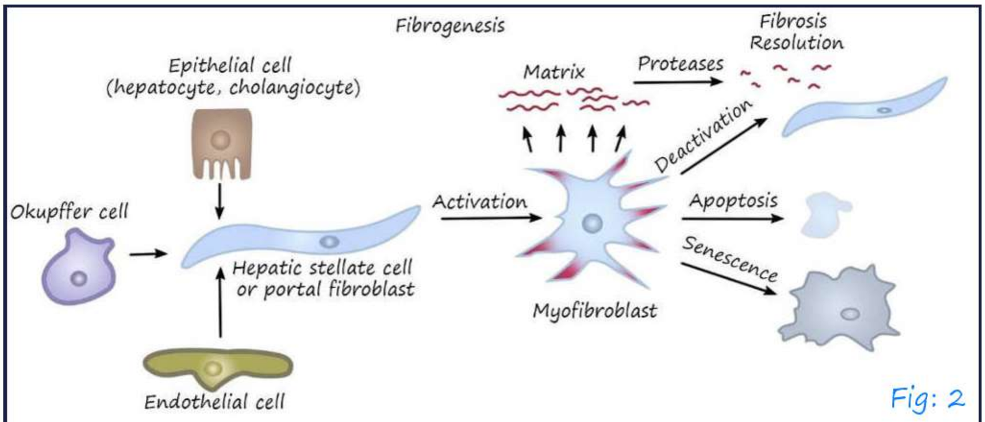

Fig: 2

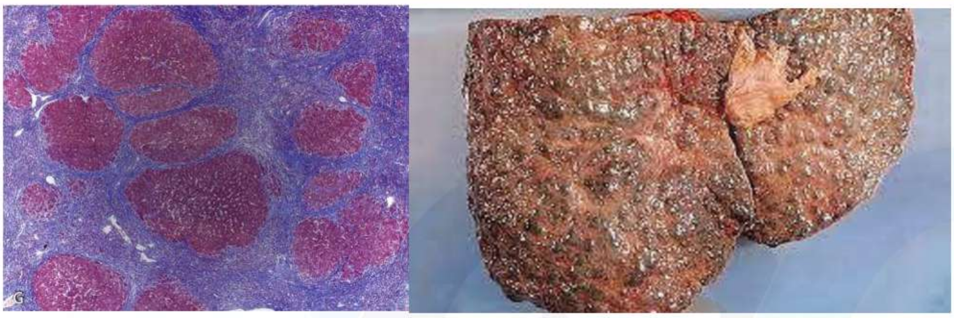

Fig: 3

- In primary biliary cirrhosis / Primary sclerosing cirrhosis } → periportal fibroblast is co converted of myofibroblast
- There is also distortion of hepatic vasculature and hepatocyte dysfunction

↓

Irreversible liver damage & Complication

Complication 00:17:25

- Portal HTN and its complication
  - Portal hypertensive gastropathy
  - Varices
  - Hypersplenism
  - Ascites → spontaneous bacterial peritonitis
- Hepatic encephalopathy

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- Hepatic coagulopathy
- Hepato-renal syndrome
- Hepato-pulmonary syndrome
- Skeletal – osteopenia & Osteoporosis
- Hematological → Anemia & Thrombocytopenia
- Malnutrition

Morphological classification of cirrhosis 00:20:42

- Micronodular cirrhosis
  - Majority of nodular < 3mm
  - Alcoholism
- Macronodular cirrhosis
  - >3 mm
  - Chronic viral hepatitis

Diagnosis 00:22:15

- Histologic diagnosis
- Clinical diagnosis'
- Lab investigation
- Imaging

Clinical feature

- 1/3 patients asymptomatic
- Non-specific features (compensated stage)

↓

  - Anorexia
  - Weight loss

- Fatigue
- Muscle cramps

- Hepatic decompensation
  - Jaundice
  - Upper GI bleed -hematemesis, melena
  - Ascites
  - Hepatic encephalopathy
- Other symptoms

  ↓

  - Hypogonadism
  - Amenorrhea
  - Irregular menstrual cycles
- Feature related to etiology

  ↓

  - Diabetes } Hemochromatosis
  - Arthropathy } Hemochromatosis
  - Cryoglobulinemia -Hepatitis c
  - Thyroiditis s- Autoimmune hepatitis

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Examination

- Hypotension (decrease MAP) → Hepatorenal syndrome
- Stigmata of CLD
- Head: - icterus

  KF ring

  Parotid enlargement (alcohol)

  Alopecia

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Fetor hepatitis

Glossitis

- Parotid enlargement due to: - fatty infiltration
  Fibrosis
  Edema
- Fetor hepaticus → sweet pungent Adour to breath
  → increase dimethyl sulfide
  → severe Porto systemic shunt
- Hands: - palmar erythema
  Clubbing → PHT, AV shunting in lung
  Dupuytren's contracture
  Nail changes -terry's nail
  ↓
  Proximal nail bed pallor
  Asterixis

Fig: 4

- Trunk: - Spider nevi
  Gynecomastia
  Loss of pubic and axillary hair
- spider nevi: - related to spider telangiectasia

Spider angioma

Prominent dilated central arteriole with branching vessels in radiating manner

3 or spider nevi -pathological

Alteration sex hormone metabolism

Other conditions: - pregnancy

Malnutrition

Number and size correlate with disease Severity

Large giant angiomas → variceal hemorrhage

- Gynecomastia: - increase production of androstenedione in

  individuals

  ↓

  Estrone

  ↓

  Estradiol

- Abdomen → Ascites

  Hepatomegaly → firm & nodular

  Splenomegaly

  Umbilical hernia

  Caput medusae

  Curvilinear Baumgarten murmur

- Caput medusae: - delated abdominal veins with flow away from

  umbilicus

  Suggest intrahepatic portal HNT

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- Curvilinear Baumgarten murmur

  ↓

  - Venous hum in epigastric area
  - Because of collateral connection

- Loss of testicular tenderness an atrophy
- Skin: - Bruises

  Itch marks

  Darkening of skin
- Hepatic encephalopathy → Flapping tremors

  B/L extensor planter

  Constructional apraxia
- Wilsons's disease: - Dystonia

  Wind beating tremor

Lab investigation

- Hypoalbuminemia'
- S bilirubin } Increase disease activity
- AST/ALT } Increase disease activity
- Increase GGT → Alcohol induces hepatic microsomal GGT
- Increase ALP
- Anemia
- Thrombocytopenia
- Viral markers

Imaging

- Ultrasonography: - surface nodularity and increase echogenicity

  Splenomegaly

  Ascites

  Screening of PHT & HCC

  Portal vein thrombosis

- Elastography: _ Transient elastography/ fibro scan

  Principle: -

  >Propagation velocity ∝ Elasticity

  - Quantification is done by kilopascals value

  > 14 KPa → Cirrhosis

  > 21 KPa → Portal HNT with complication

- Liver biopsy: - Gold standard for diagnosis

Why it is done?

- Demonstrate the presence of cirrhosis
- Etiology
  - Wilson's disease
  - hereditary hemochromatosis

Scoring systems 01:0054

- Assessing compensated /decompensated
- Prognostic
- Child Pugh scoring system

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Child-Pugh Classification of Cirrhosis				
	POINTS TOWARD TOTAL SCORE			
FACTOR	units	1	2	3
Serum bilirubin	umol/L mg/dL	<34 <2.0	34-51 2.0-3.0	>51 >3.0
Serum albumin	g/L g/dL	>35 >3.5	30-35 3.0-3.5	<30 <3.0
Prothrombin time	seconds prolonged INR[a]	<4 <1.7	4-6 1.7-2.3	>6 >2.3
Ascites		None	Easily controlled	Poorly controlled
Hepatic encephalopathy		None	Minimal	Advanced

- Score 5-15
- Child Pugh A (CPA) → score 5&6 – compensated stage
- Child Pugh B (CPB) → score 7-9 – decompensated state
  - Candidate for liver transplant
- CPC → 10 to 15
- MELD Na score: - Model for end stage liver disease
- Includes – S. bilirubin
  - INR
  - Creatinine

MELD Na score

- MELD + Serum Na+
- Predicting prognosis to liver transplant

PELD score

- Children < 12 year

Histologic scoring system

- METAVIR scoring system
- Ishak Scoring System
- Histology activity index.

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OVERVIEW OF PORTAL HYPERTENSION

Normal hepatic circulation 00:01:59

- Liver – dual blood supply
  - Portal vein
  - Hepatic blood
- Portal venous blood →75% of total hepatic blood flow
- 25 % of hepatic blood flow is from hepatic artery
- Converge at hepatic sinusoids
- High compliance and low resistance system

Portal venous system 00:06:13

- Formed by splenic vein and superior mesenteric vein behind neck of pancreas
- At hilum of liver → divides into RIGHT and Left branches
- Umbilical vein drains into Left portal vein
- Cystic vein drains onto Right portal vein
- Portal venules are drains into hepatic sinusoids

↓

Via hepatic veins →IVC

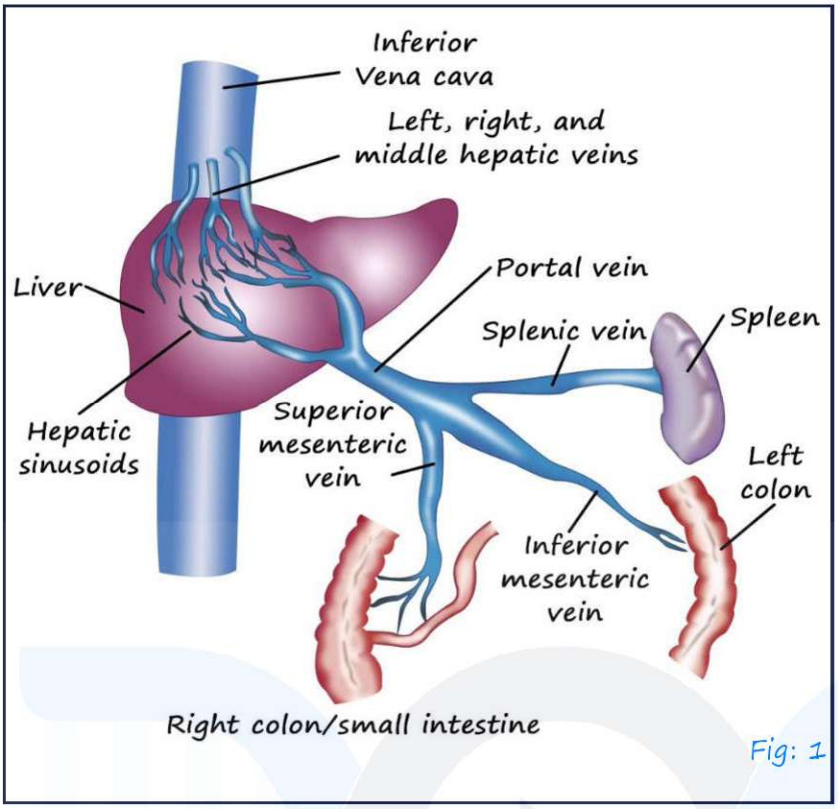

Fig: 1

Hepatic sinusoids 00:11:49

- These are highly permeable
- Helps in transport of macromolecule to hepatocytes
- Reason for permeability
  - Fenestrated endothelium
  - Lack a proper basement membrane

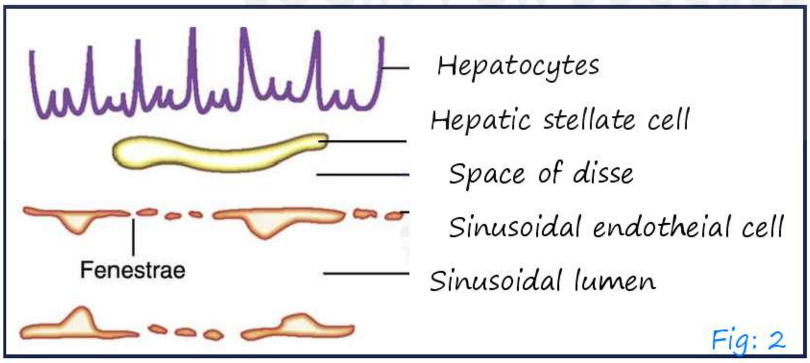

Fig: 2

- In cirrhosis, there occurs alteration in hepatic microcirculation
  - Loss of normal fenestration (De-fenestration)

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- Constriction of sinusoids
- Hepatic stellae cell activation

↓

ECM matrix deposition happens

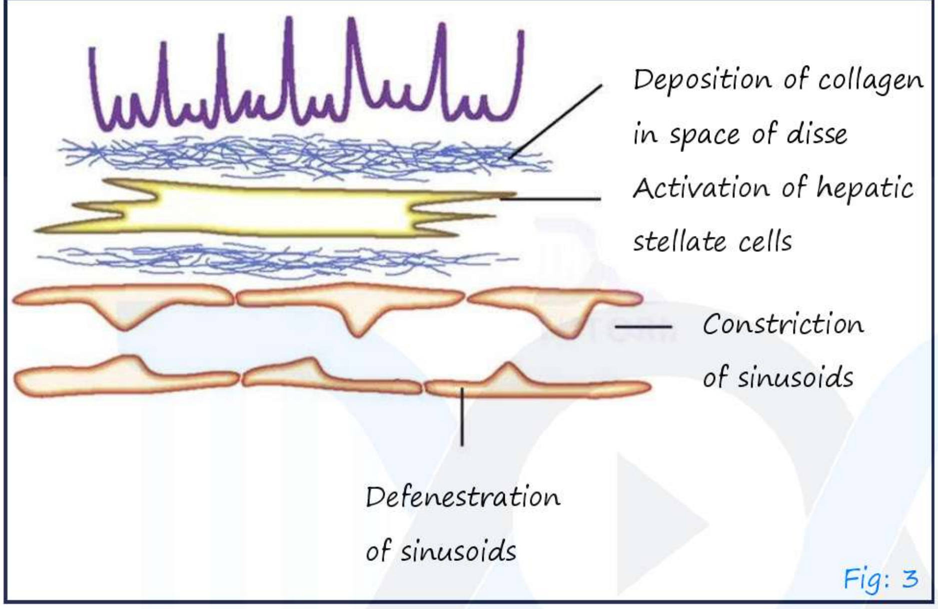

Fig: 3

Hepatic arterial buffer response 00:19:00

- Total hepatic blood buffer flow – constant
- Autoregulatory mechanism

Portal HTN 00:21:15

- Resistance to portal blood glow
- Hepatic sinusoids pressure ≥ 6 mm Hg

  Hypertensive hepatic sinusoids
- Resistance can occur @ different sites
  - Pre-hepatic
  - Hepatic → cirrhosis

- Post – hepatic

Etiology 00:24:59

I Pre- hepatic causes

- Portal vein thrombosis
- Splenic vein thrombosis

II Hepatic causes

- Pre sinusoidal
- Sinusoidal
- Post sinusoidal

Pre sinusoidal ↓

- Sarcoidosis
- Schistosomiasis
- Primary biliary cirrhosis
- Sinusoidal → Alcohol related cirrhosis
  Cryptogenic cirrhosis
- Post sinusoidal → sinusoidal obstruction syndrome

III post hepatic causes

- Budd Chiari syndrome
- Constrictive pericarditis
- IVC obstruction
- Right sided heart failure
- Tricuspid regurgitation

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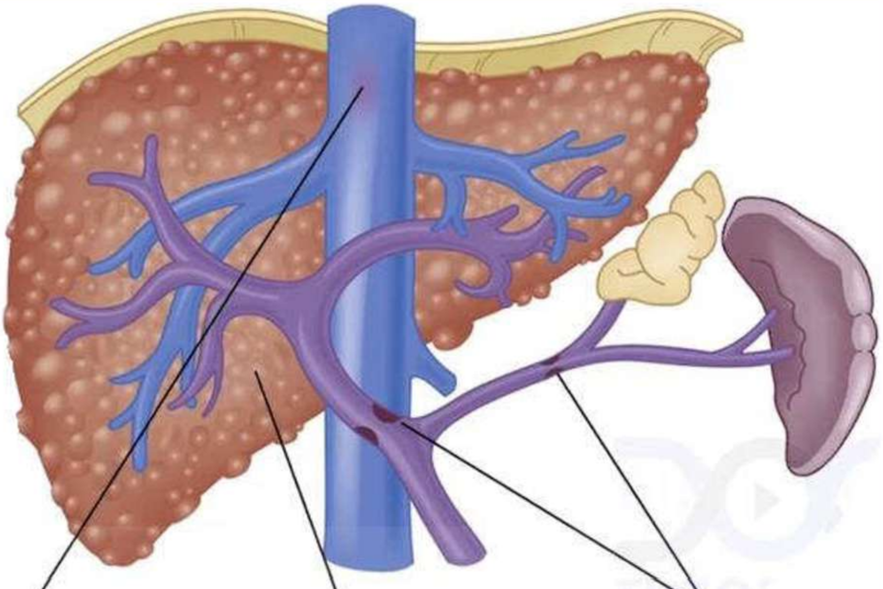

Fig: 4

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Classification of Portal Hypertension

Prehepatic

- Portal vein thrombosis
- Splenic vein thrombosis
- Massive splenomegaly (Banti's syndrome)

Hepatic

- Presinusoidal

Schistosomiasis

Congenital hepatic fibrosis

Sinusoidal

Cirrhosis-many causes

Alcoholic hepatitis

Postsinusoidal

Hepatic sinusoidal obstruction

(venoocclusive syndrome)

Posthepatic

Budd-Chiari syndrome

Inferior vena caval web

Cardiac causes

Restrictive cardiomyopathy

Constrictive pericarditis

Severe congestive heart failure

- Why this increased resistance?

Structural reasons | Dynamic reasons

↓

- Hepatic microcirculation affection due to – fibrosis
  - nodule
  - angiogenesis
  - vascular osculation

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- Dynamic factors

↓

- Increase vasoconstrictors → Endothelin's
  → Thromboxane
  → Angiotensin II
  → Nor – epinephrine
- Decrease vasodilators → Nitric oxide
- Splanchnic blood flow increased due to No VEGF

↓

Further worsens portal HTN

Basics hemodynamic changes

- ΔP= FXR
- ΔP= pressure gradient in portal circulation
- F= portal blood flow
- R= resistance to flow
- Increased portal blood flow

↓

- Peripheral and splanchnic vasodilation
- Increase cardiac output
- Results in hyperdynamic circulatory state

- Increase in resistance

↓

Structural and dynamic factors

- Once portal HTN sets in

↓

Collateral vessels

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- Communication /connections between
  - High pressure portal system
  - Low pressure systemic veins

↓

Complication of portal HTN

Site of collateral formation 00:44:00

- Distal esophagus and proximal stomach
- Umbilicus (caput medusae)
- Rectum
- Retroperitoneum

How to measure portal pressure

- Indirect (most common)
- Direct

Indirect (most common) ↓

- Hepatic vein pressure gradient (HVPG)
- Splenic pulp pressure } direct
- Portal vein pressure } direct
- Transient elastography and MR elastography

↓

Indicate presence of portal HTN

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HPVG

- Calculated as difference between WHVP and EHVP
  - WHVP – wedged hepatic venous pressure
  - FHVP- Free hepatic venous pressure

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- One of best predictors
- HVPG ≥ 6 mmHg: - portal HTN
- Problem – not effective when portal HTN due to presinusoidal causes

Type of Portal Hypertension	WHV	FHVP	HVPG
Prehepatic	Normal	Normal	Normal
Presinusoidal	Normal	Normal	
Sinusoidal	Increased	Normal	Increased
Postsinusoidal	Increased	Normal	Increased
Posthepatic			
Heart failure	Increased	Increased	Normal
Budd-Chiari syndrome	-	Hepatic vein cannot - be cannulated	-

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Clinical features 00:54:13

- Asymptomatic
- Esophageal or gastric varicella bleed
  - Hematemesis
  - Melena
- PHG - portal hypertensive gastropathy → mosaic pattern

- GVE – gastric vascular ectasia
  - ↓ Mucosal changes
  - → Aggregate of ecstatic vessels
- Chronic blood loss – anemia
- Stigmata of chronic liver disease
- Other cardinal finding → splenomegaly
  → Abdominal collateral vessels
  → Thrombocytopenia

Complication 00:59:15

- Variceal hemorrhage
- PHG
- Ascites -> spontaneous bacterial peritonitis
- Hepato renal syndrome
- Hepatopulmonary syndrome
- Hepatic hydrothorax
- Porto pulmonary HTN
- Cirrhotic cardiomyopathy
- Portal cholangiopathy

Evaluation 00:01:59

- OGD scopy: – To look for varices
- Reporting of varices → Japanese Research society
  ↓
  Parameters are – red color signs

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↓

radish patches

cherry red spots

Colors

Size

Location

- Grading of varices
  - Grade I: – small and straight
    - II: – tortuous occupies < 1/3 of esophageal lumen
    - III: – large, occupies > 1/3rd of esophageal lumen

Utility of ultrasound with doppler

- Splenomegaly
- Porto systemic collateral vessels
- Hepatic fugal flow
  - Reversal of direction of flow in portal vein.

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TREATMENT OF PORTAL HYPERTENSION

Treatment of Portal HTN 00:00:30

- Reducing portal flow
- Decreasing intrahepatic resistance

Pharmacologic agents 00:02:33

1.Drugs that decrease portal flow

- Non – Selective β blockers
  - Nadolol
  - propranolol
- Somatostatin analogues
- Vasopressin, terlipressin

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2.Drugs that reduce intrahepatic resistance

- Nitrates
- α receptor blockers – Prazosin
- Angiotensin receptor blockers

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Vasopressin

- Causes splanchnic vasoconstriction
- Decreases portal venous flow
- Decreases portal pressure
- Significant side effects
  - Bowel necrosis
  - Negative ionotropic and chronotropic action

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Terlipressin

- Semi synthetic analogue
- Better safety profile

Somatostatin and analogues

- T ½: - 1-3 minutes
- octreotide
- Larazotide
- Vapreotide

(octreotide, Larazotide, Vapreotide) → decrease portal pressure

Non – selective beta blockers

- Decrease portal pressure

  ↓

  Decrease cardiac output

  Decrease portal flow
- Propranolol, nadolol
- Carvedilol – combined α + β blockade

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Nitrates

- Act by causing venodilation

Endoscopic therapy 00:15:02

- Prevention of variceal bleeding
- Control of acute variceal bleeding
- Prevention of variceal re – bleeding
- Can be used for variceal sclerotherapy band ligation

Variceal sclerotherapy

- Injection of sclerosant → intravesical / Para – variceal
- Common sclerosants
  - Sodium tetradecyl sulfate
  - Ethanolamine oleate
  - Alcohol

Variceal ligation (EVL)

- Better method
- Deploy a band around varix

  ↓

  Strangulation and thrombosis

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Balloon tamponade 00:19:16

- Sengstaken Blakemore
- Minnesota tube

] temporary method before TIPS

↓

Transjugular – Intrahepatic portosystemic shunt

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TIPS 00:20:19

- Done by interventional radiologist
- Communication is established between intrahepatic branch of portal vein and hepatic vein
- Most common indication – refractory variceal bleeding

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Surgical procedures 00:21:53

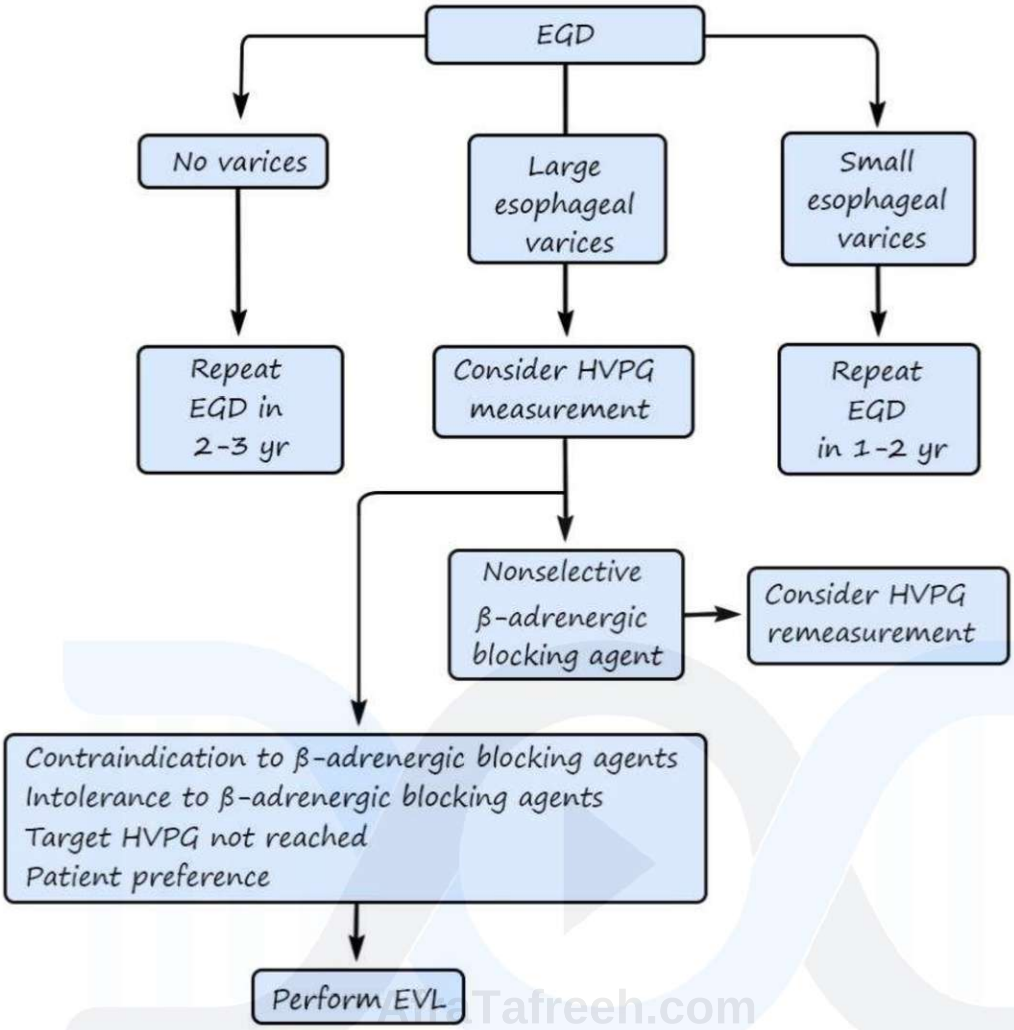
- Porto – systemic shunt procedures
- Non shunt procedure
- Liver transplantation

Esophageal varices 00:23:12

- 40% of cirrhosis patients will have esophageal varices
- 60% of cirrhosis + ascites will have esophageal
- 25% chance of a varix to bleed in 2 years
- Predictors of bleedings
  - Variceal size
  - HVPG
  - Risk of bleeding nil when HVPG is <, 12 mm Hg
- Treatment
  - Primary prophylaxis
  - Control of acute variceal bleeding
  - Secondary prevention or re – bleeding

Primary prophylaxis

- Large varix (diameter > 5 mm)
- Long-acting Propranolol / nadolol



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Control of acute bleeding

- Priorities
  - Resuscitate the patient
  - Control bleeding
  - Prevent complications
- Secure 2 large bore IV lines
- RBC transfusion when Hb < 7g%
- Achieve hemodynamic stability with saline
- Active bleeding → airway protection ET intubation
- Antibiotics → oral – Norfloxacin 400 mg BD X 7 days

  Parenteral – ceftriaxone 1g iv OD x 7 days

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- Vasoactive pharmacologic therapy

  ↓

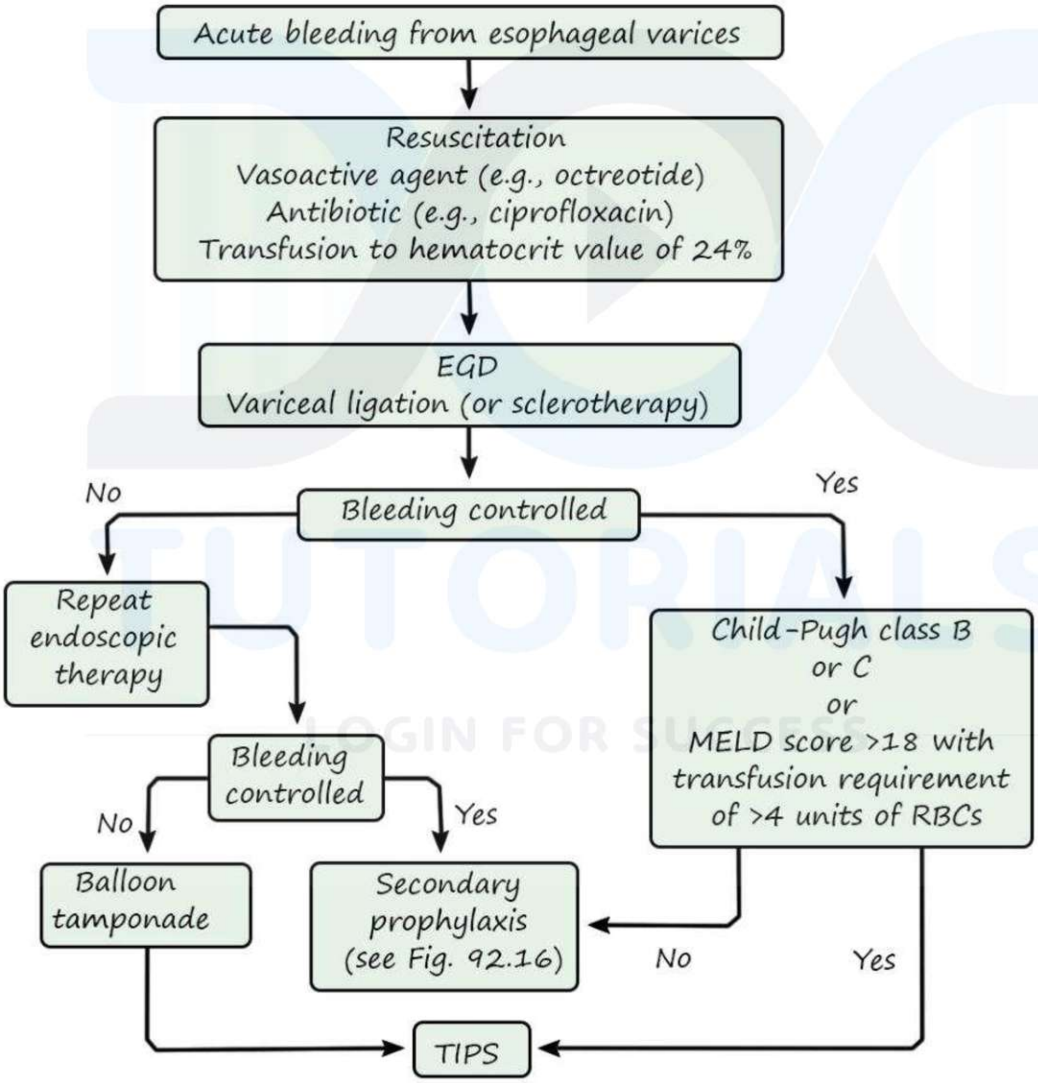
  Somatostatin / vasopressin analogues

  Terlipressin preferred

  ↓

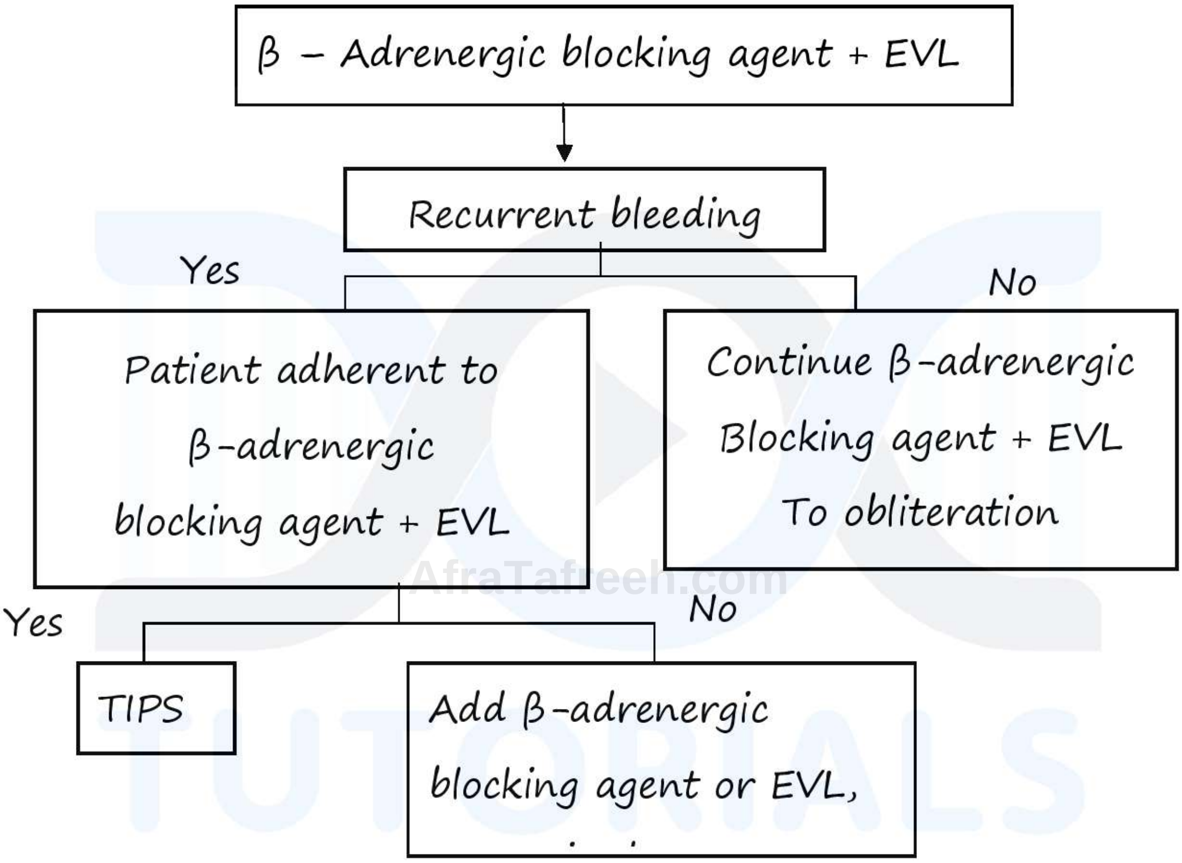
  Should be started as early as possible

- Endoscopic therapy → EVL → ligate the actively bleeding varix



Prevention of Re-Bleeding

- All patients with variceal bleed → go for 2° prophylaxis
- Preferred initial option → EVL + Non selective β blockers.



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HEMOCHROMTOSIS

- Refers to group of iron storage disorders
- Predisposition to develop iron overload
- Can progress to fibrosis and organ failure

Basics of Iron Metabolism 00:02:29

- Total body iron pool: - 3-4 gram
- Mucosal iron absorption = Iron loss
- 1mg /day – males
- 1.5 mg/day – menstruating females
- Regulating of iron homeostasis
  ↓
  At the level of absorption
  (Not excretion)
  — Unique property
- Major site of iron absorption – Duodenum

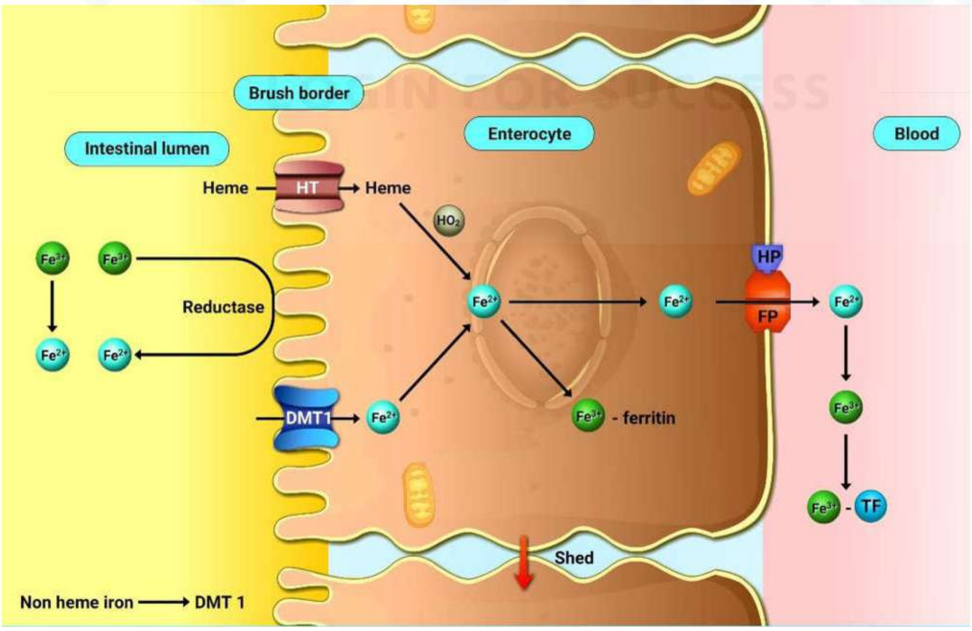

Fig: 1

- Fe2+ crosses basolateral side by a transporter ferroportin (FP)
- Hephaestin will assist ferroportin

  ↓

  Also aids conversion of $Fe^{2+} \rightarrow Fe^{3+}$
- One transferrin molecule binds to 2 molecules of iron

Hepcidin

- Plays chief role ion iron homeostasis
- Encoded by HAMP gene
- Produced and secreted by liver
- Down regulates and internalizes ferroportin
- Other genes that regulate hepcidin synthesis
  - HFE
  - Hemojuvelin
  - TRF 2

  } maintaining N hepcidin levels

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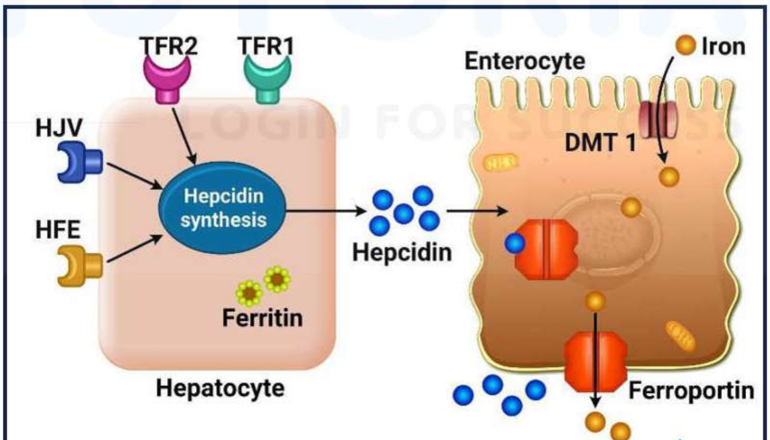

Fig: 2

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Iron overload states 00:18:01

1o hemochromatosis (Or) Hereditary	2o hemochromatosis (Or) Acquired iron overload

Classification of Iron Overload States
Hereditary Hemochromatosis
Hemochromatosis, HFE-related (type 1)
C282Y homozygosity
C282Y/H63D compound heterozygosity
Hemochromatosis, non-HFE-related
Juvenile hemochromatosis (type 2A) (hemojuvelin mutations)
Juvenile hemochromatosis (type 2B) (hepcidin mutation
Mutated transferrin receptor 2, TFR2 (type 3)
Mutated ferroportin 1 gene, SLC11A3 (type 4)

Acquired Iron Overload	
Iron-loading anemias	Chronic liver disease
Thalassemia major	Hepatitis C
Sideroblastic anemia	Alcoholic cirrhosis, especially when advanced
Chronic hemolytic anemias	Nonalcoholic steatohepatitis
	Porphyria cutanea tarda

Transfusional and parenteral iron overload Dietary iron overload	Dysmetabolic iron overload syndrome Post-portocaval shunting

Hereditary hemochromatosis

HFE related | Non HFE related

HFE related ↓	Non HFE related ↓
• HFE gene – chromosome P • Most common gene mutation– c282 y other mutation – H63 D • autosomal recessive • Age: - 40-60 years • Northern Europe	• Hemojuvelin • TFR 2 mutation] gene mutation • Ferroportin • Juvenile hemochromatosis • No genetic prediction

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Pathogenesis

- Final common pathway of both HFE related and non HFE related – Hepcidin pathway
- Increased iron absorption (> 4 mg/day)

↓

Progressive iron accumulation and parenchymal iron deposition

- m/c organ involved – liver

↓

Due to – lipid peroxidation

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- stimulation of collagen synthesis
- ROS and iron interact with DNA

↓

Cell injury

- Disease manifest when iron store > grams
- Severe hemochromatosis → Iron store > 50 grams
- End result in liver – fibrosis
  - Fibrosis
  - Macro – nodular
  - Mixed micro + macro nodular
- Other organs involved in hereditary hemochromatosis

↓

- Pancreas
- Heart
- Skin
- Joint
- Endocrine glands (pituitary, adrenal, thyroid)

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Clinical manifestation 00:30:23

- General predisposition → no other symptoms
  Non biochemical abnormality
- Iron overload → but without symptoms
- Iron overload and early symptoms
- Iron overload with organ damage – cirrhosis
- <u>Liver:</u> m.c organ involved

- Hepatomegaly > 95% of symptomatic individuals
- Partial HYN and esophageal varices – less common
- 30 % of cirrhosis patients develop hepatocellular carcinoma

↓

Men, alcoholic

- Skin: feature of advanced disease
  - Metallic /state grey pigmentation → Bronze presentation
  - Increased melanin and iron in dermis
- Diabetes: - destruction of pancreatic islets
  - advanced disease

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Joint involvement

- 25-50% of symptomatic patients
- m/c joint: 2nd and 3rd MCP joints
  - joint space narrowing
  - subchondral cyst formation chondrocalcinosis
  - osteopenia
  - joint swelling

Cardiac involvement

- m/c manifestation – chronic cardiac failure
- dilated cardiomyopathy >> restrictive
- cardiac arrhythmias

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Hypogonadism → hypogonadotropic hypogonadism

- Increased susceptibility to infection by iron loving or siderophilin bacteria

  ↓

  - vibrio vulnificus
  - L. monocytogenes
  - Y. enterocolitica
  - Y. pseudotuberculosis

Diagnosis 00:44:35

- High index of clinical suspicion
- Assessment of iron stores

  ↓

  - Percentage saturation transferrin

    $\frac{\text{S. iron}}{\text{TIBC}} \times 100$ ↑↑

  - Serum ferritin ↑↑
  - Liver biopsy → Iron concentration

    → Hepatic iron index

  - MRI

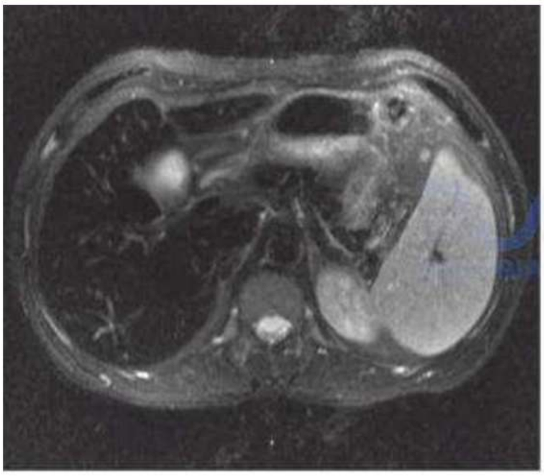
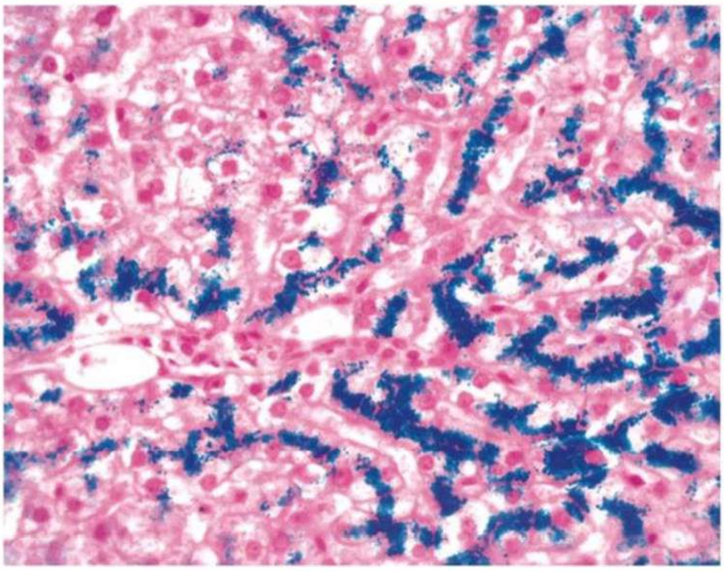


Fig: 3



Perl's Prussian blue staining Fig: 4

- Screening: – % saturation o transferrin + serum ferret

  + > 300 mg/L
- Confirmation by Genetic Analysis (HFE gene mutation)

  ↓

  C282 Y

  H63 D

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Treatment 00:53:13

- Remove excess iron from body
- Supportive treatment

Phlebotomy: – weekly

- 1-unit whole blood – 200 – 250 mf iron
- Hematocrit should not go below
- 2-3 monthly check ferritin and transferrin saturation

  (< 100 mg/L) (<50%)

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- Once target achieved – monthly 2-3 phlebotomies
- Joint damage
- Hypogonadisms

(Joint damage and Hypogonadisms: Usually does not improve)

Iron chelators → Deferoxamine – subcutaneous injection
↓
5 days a week
→ Deferasirox – oral iron chelator
→ Phlebotomy > Iron chelators

- End stage liver disease – liver transplantation.

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AUTOIMMUNE HEPATITIS

- Progressive immune mediated chronic hepatitis of unknown cause, characterized by:
  - Genetic predisposition
  - Auto antibodies
  - Hypogammaglobinemia
  - Histologic features – interface hepatitis & Lymphoplasmacytic infiltrate

Etiopathogenesis 00:03:26

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- Loss of immune tolerance to self-antigen
- Strong association with certain HLA alleges → DR3, DR4, DRB1
- ? Infections, drugs, toxins
- Lymphocytic infiltrate is composed of CD4 + T cells
  - ↙ CD8 + T cytotoxic cells
  - Activate B cells → antibody Producing plasma cells

Morphological changes 00:07:25

- Interface hepatitis: - Inflammation at the interface
- Hepatic parenchyma and connective - Tissue around portal tract
- Periportal necrosis: - piecemeal necrosis
- Emperipolesis: - Lymphocyte in the cytoplasm of damaged Hepatocyte

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- Russeting of hepatocytes

Clinical features 00:11:35

- Asymptomatic
  - Elevated transaminases
  - 25 %
- Chronic nonspecific symptoms
  - Fatigue
  - Malaise
  - Arthralgia
  - Nausea
- Acute onset of symptom
  - Jaundice
- Acute sever /fulminant presentation
- Cirrhosis with or without hepatic decompensation
- Extra -hepatic autoimmune disease
- Overlapping disease: - primary biliary cirrhosis
  Primary sclerosing cholangitis

Type I Autoimmune hepatitis 00:18:04

- 90 % cases
- Autoimmune: - Anti smooth muscle antibody (ASMA)
  Anti – actin antibody
  ANA
  Anti SLA (soluble liver antigen) / anti LP
  HLA association – DR3, DR3, DR13
- Any age of onset → young middle-aged females

- Females > Males
- Variable clinical and histopathologic severity
- Also associated with autoimmune disease
  - Autoimmune thyroiditis
  - Grave's disease
  - SLE
  - Rheumatoid arthritis
  - Celiac disease
  - Ulcerative colitis
  - Comb's +ve hemolytic anemia
  - Autoimmune thrombocytopenic purpura
  - Symptomatic cryoglobulinemia

Type 2 Autoimmune hepatitis 00:25:20

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- 10% of AIH
- Autoantibodies: - Anti LKM -1 (liver-kidney – microsome)
  Anti LC-1 (liver – cytosol)
  Anti LKM -3
  - LKM -1 – chronic hepatis C
  - LKM -2 Drug induced hepatitis
  - LKM -3 Hep.D
- HLA DR3 and DR7 association
- Onset: - childhood and young adulthood → Mostly < 14 years
- Clinical & histopathologic severity → And advanced
- Associated with autoimmune diseases
  - Autoimmune thyroiditis

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- Diabetes
- Vitiligo

Examination 00:30:54

- Hepatomegaly ++
- Splenomegaly +
- 25 % patients have normal physical examination

Investigation 00:31:53

- Elevation in serum ALT, AST
- Elevation in gamma globulins'
- Elevation in serum IgG level

  N IgM & Ig A
- Hyperbilirubinemia
- Elevation in serum ALP
- Elevation in serum GGT
- Autoantibodies → ASMA

  → ANA

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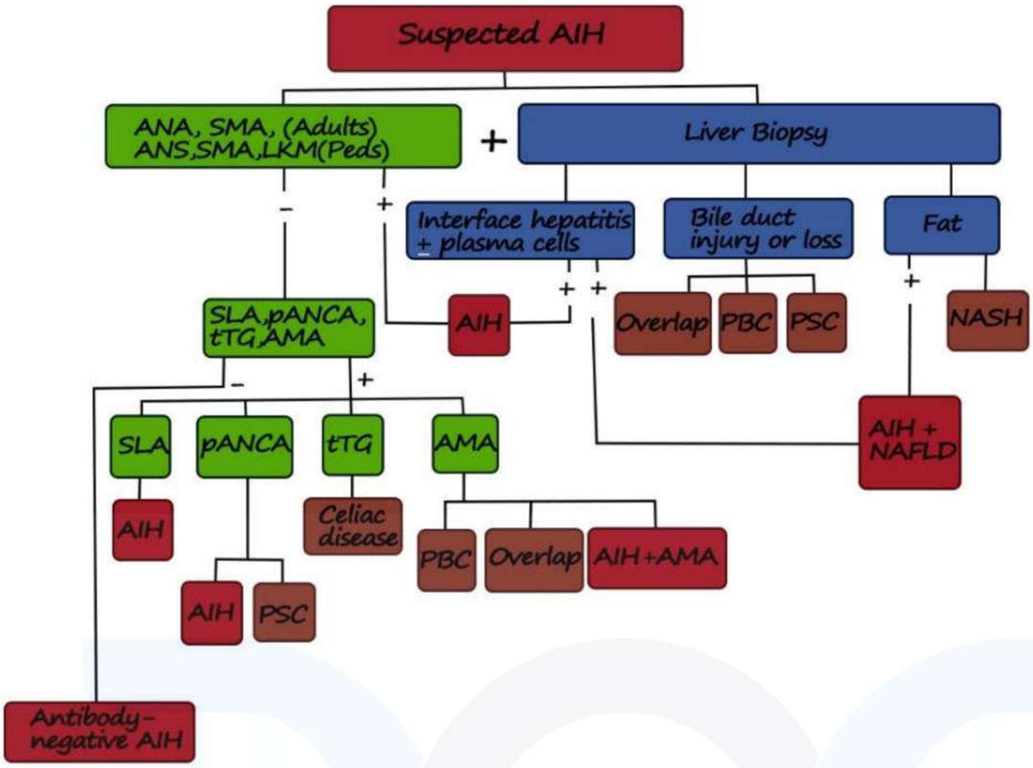

AASLD 2019 guideline

- Liver biopsy

Exclude diseases with similar presentation

- Wilson's disease
- NAFLD
- DILI
- Chronic viral hepatitis

		Points
Autoantibodies	ANA or ASMA or LKM > 1:80 ANA or ASMA or LKM > 1:40 SLA/LP Positive (>20 Units)	2 1 0

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IgG (Or gramma globulins)	>1.10 times normal limit Upper normal limit	2 1
Liver histology	Typical for autoimmune hepatitis compatible with autoimmune hepatitis atypical for autoimmune hepatitis	2 1 0
Absence of viral hepatitis	Yes No	2 0

Total score ≥ 7 - definite autoimmune hepatitis

6 – probable autoimmune hepatitis

Treatment 00:41:26

- AASLD -2019 guidelines
  - Prednisone /prednisolone + azathioprine
  - Do TMPT activity if possible
  - Alternate to azathioprine- MMF
  - Induction phase: - 4-8 weeks
  - Maintenance phase: -
  - Biochemical remission +: - AST, ALT, gamma globulin

↓

Taper drug

- Better response to treatment → Type I AIH

- If the patient has biochemical remission and no symptoms for 2 years → stopping of drugs

Newer agents

- Abut TNF – α: - Infliximab
- Anti-CD 20: - Rituximab
- Cirrhosis with decompensation – liver transplantation
- Recurrence of AIH following liver transplantation

Variable	Type 1 Autoimmune Hepatitis	Type 2 Autoimmune Hepatitis
Characteristic autoantibodies	Antinuclear antibody Smooth muscle antibody Anticalin antibody Autoantibodies against soluble liver antigen and liver-pancreas antigen Atypical perinuclear antineutrophil	Antibody against liver-kidney micro some 1 Antibody against liver cytosol 1

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	cytoplasmic antibody	
Geographic variation	Worldwide	Worldwide; rare in North America
Age at presentation	Any age	Predominantly childhood and young adulthood
Sex of patients	Female in approximately 75% of cases	Female in approximately 95% of cases
Association with other autoimmune diseases	Common	Common
Clinical severity	Broad range	Generally severe
Histopathologic features at presentation	Broad range	Generally advanced
Treatment failure	Infrequent	Frequent
Relapse after drug withdrawal	Variable	Common
Need for long-term maintenance	Variable	Approximately 100%

OVERVIEW OF ASCITES

Ascities

- Abnormal accumulation of fluid in peritoneal cavity.

Etiology of ascites 00:01:10

1. Liver cirrhosis
   - 60% of patients with cirrhosis 10 years → ascites
2. Cardiac failure
3. Tuberculosis
4. Malignancies
   - 1° peritoneal malignancies
   - Breast ca (Eg: Mesothelioma, sarcoma)
   - Lung ca
   - Colon ca
   - Stomach ca

   - Mechanism of ascites in malignancy:

     i. Protein rich fluid → secreted by tumor cells

     ii. Fluid shift from ECS → Peritoneum
5. Pancreatic diseases
6. Hypothyroidism
7. Familial Mediterranean fever

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Pathogenesis of ascites in liver cirrhosis 00:06:28

1. Portal hypertension

2. Renal sodium retention

- Due to activation of RAAS and Sympathetic nervons system

↓↓

Renal sodium retention

↓↓

Expansion of ECF volume

↓↓

Ascites and edema

Why? Functional renal derangements?

Splanchnic arterial vasodilatation

Functional renal derangements 00:09:40

1. Impaired ability to excrete sodium (Earliest)

- Ascites and edema

2. Impaired ability to excrete solute free water

- Dilutional hyponatremia

3. Reduction in GFR (due to renal vasoconstriction)

- Hepato renal syndrome

Chronic inflammatiory state → splanchnic vasodilatation

Sodium retention 00:13:00

To achieve negative sodium balance

↓↓

By increasing urinary sodium excretion

↓↓

Goal of pharmacological therapy for ascites in liver cirrhosis

Difficult to control ascites	Mild – Moderate Ascites
U. Sodium excretion	U-sodium excretion
<10 meq/day	>10 meq/day

Renal handling of sodium

95% of filtered sodium → Reabsorbed by renal tubules

Reabsorption

- 60-70% → In proximal tubule s
- 30-40% → In thick ascending limb
- 5-10% → In collection duet

Both proximal and distal tubules → Role in Na^+ retention

Portal hypertension

- Initiating factor for splanchnic arterial vasodilatation
- Factors responsible

1.No

2.Endocannabinoids

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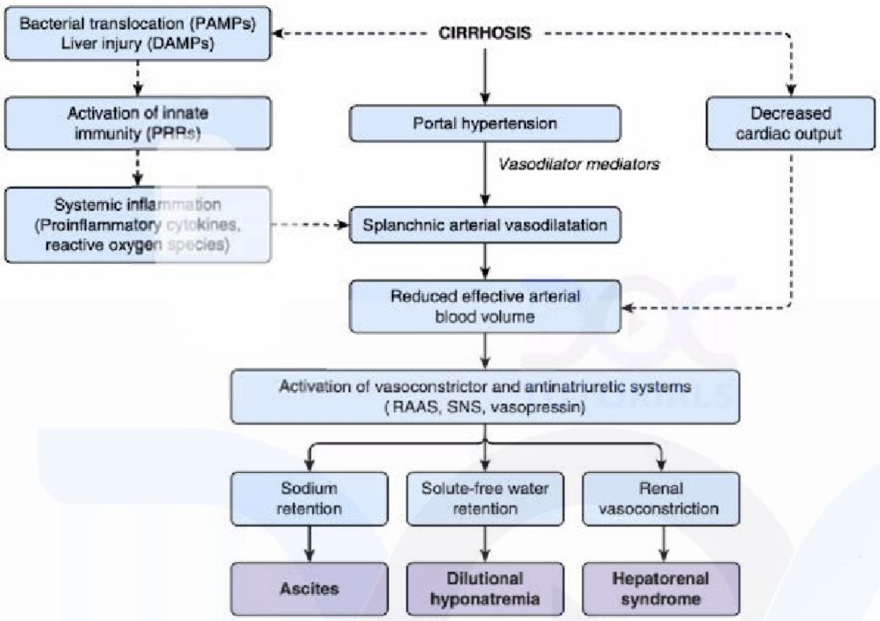
- End result: Reduction in effective arterial blood volume



Complications 00:22:30

1. Spontaneous bacterial peritonitis
2. Hyponatremia
3. Acute kidney injury
4. Refractory ascites
5. Hepato renal syndrome

Diagnostic evaluation 00:23:20

1. Confirm diagnosis of CLD
2. Rule out other causes of ascites

History
↓
Physical examination
↓
Lab evaluation

Grading of ascites 00:25:48

Grade 1: Mild ascites	USG is diagnostic
Grade 2: Moderate ascites	Physical examination is diagnostic
Grade 3: Large ascites	Inspection

Recurrent ascites 00:27:25

- Ascites that recurs atleast 3 times in 1 year period despite appropriate treatment

Lab investigations 00:28:20

1.Blood routines

2.Urinary Na excretion

- 24 hours arine Na . spot sample
- If Na excretion:
  - <10 meq/day i.e sodium retention
  - Median survival time is only 1 year

3.Abdomial ultrasound

- Liver parenchymal echoes
- Patency of portal vein / Hepatic vessels
- Rule out malignancy

4.Ascitic fluid analysis

- Help in differentiating ascites from other differentials
- Detects ascitic fluid infection

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Method: Diagnostic paracentesis

1.Absolute neutrophic count (ANC)

2.Colour

3.Total protein

4.Albumin

5.Culture

ANC >250/mm³ --. SBP (Diagnostic)

Ascitic fluid protein → Role in prognosis

↓↓

<1.5g/dl → risk of SBP

Culture → min (10ml) required

In SBP → Monomicrobial

(Spontaneous Bacterial peritonitis)

In secondary bacterial peritonitis → Polymicrobial

SAAG 00:37:35

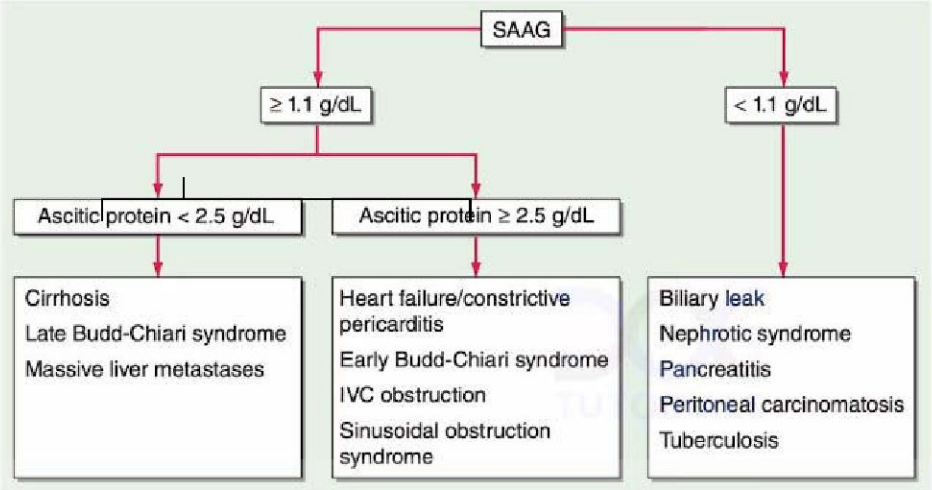
- Serum ascites albumin gradient
- Determines whether ascites is due to portal hypertension
- SAAF

  1.Reflects pressure within hepatic sinusoids

  2.Corresponds to HVPG
- SAAF > 1.1gm/dl (i.e 1/gm/l)

  - 97% due to portal hypertension
- SAAF <1.1gm/dl

  - Unlikely portal hypertension



Patients with high SAAG ascites

Ascitic fluid protein level

<2.5 g/dl	>2.5 g/dl
↓↓	↓↓
Damaged hepatic sinusoids	normal hepatic sinusoids

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Secondary bacterial peritonitis 00:44:50

- Glucose /LDH/Amylase / Lipase → Role in diagnosis
  ↓↓ ↓↓
  Decrease increase
- Gram staining → Polymicrobial
- In TB ascites → Gene xpert/culture
- In malignancy → ascites fluid cytology (Specific but less sensitivity)
- In peritoneal carcinomatosis → increase ascites fluid cholesterol

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Chylons ascites 00:49:20

- White, milky ascitic fluid
- Triglyceride level > 200mg/dl
- Cause: Lymphatic Disruption

  Trauma   cirrhosis   TB   Malignancy

- Dark brown fluid ascites → Biliary tract perforation
- Black fluid → metastatic melanoma.

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MANAGEMENT OF ASCITES

Uncomplicated ascites	**Complicated ascites**
Treatment depends on grade of ascites	1. Refractory ascites 2. Spontaneous bacterial peritonitis 3. Hepatorenal syndrome (any of above)

Management of uncomplicated ascites 00:03:04

- Managed on OP basis
- Aim: To achieve negative sodium balance

Decrease sodium intake | increase renal sodium excretion (Diuretics)

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Grade 1 ascites: No treatment required

Grade 2 ascites: 1 Diuretics

(Normal GFR; U Na^+ excretion → >20meq/L)

- Fluid restriction not necessary – In 1st presentation with grade 2 ascites

"Dietary restriction"

– Might be sufficient

Dietary Na → 0-120 meq/day

↑↓

4.6-6.9 gm/day

Therefore, patient is advised to not to take added salt (Eg: Pickles)

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Diuretics used:

1. Anti-mineralocorticoids (1st line)
   - Spironolactone
   - Eplerenone

- Slow mechanism of action
- For a particular dose of diuretic to show its action 72 hours in required
- Loop diuretics: Not used alone
  Given with anti-mineralocorticoids

1st episode of ascites: Anti Mineralocorticoid

- Spironolactone 100mg/day
  ↓ if not responding for 3 days
  100 mg increments
  But max dose 400 mg/day
- Complication: Hyperkalemia
  ↓ If not responding
  Loop diuretics
- Frusemide 40mg/day
  ↓ If not responding
  40 mg increments
  But max dose 160 mg/day

Management of Grade 2 (Moderate) Ascites
DIET Low-sodium diet (80-120 mEq/day) **DIURETICS** First episode of ascites: Spironolactone, 100 mg/day; increase in a stepwise manner every 72 hr according to treatment response to a maximum dose 400 mg/day If no response or hyperkalemia develops, add furosemide, 40 mg/ day, increasing in a stepwise manner to a maximum dose of 160 mg/day Recurrent ascites: Combination diuretic treatment with spironolactone and furose mide (same doses as above) **MONITORING** Daily body weight (recommended body weight loss is up to 0.5 kg/ day in patients without edema and 0.5-1 kg/day in patients with ascites and edema) Once ascites has been mobilized, continue a low-sodium diet and the minimum diuretic dose necessary to avoid reaccumulation of ascites

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Grade 3 ascites:

- T.O.C → Large volume paracentesis

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Risk of developing PPCD (Post Paracentesis circulatory Dysfunction)

- Further decrease in arterial blood volume (effective)
- Rapid reaccumulation of ascites
- Risk of hepatorenal syndrome
- If large volume paracentesis is to be performed,
- Plasma volume should be replaced to avoid PPCD
- If >5 litres removed → 20% iv albumin
- If < 5 litres removed → 20% iv albumin + saline

Management of Grade 3 (Tense) Ascites
DIET Low-sodium diet (80-120 mEq/day) LARGE-VOLUME PARACENTESIS IV albumin should be administered (8 g per L of ascites removed) DIURETICS The minimum diuretic dose necessary to avoid accumulation of ascites should be continued If the patient has not received diuretic treatment previously, start with spironolactone, 100 mg/day, and furosemide, 40 mg/day If the patient was receiving diuretic treatment, restart diuretics at a higher dose. If there is no response to treatment, assess the patient's sodium intake for adherence to a low-sodium diet, and increase the diuretic doses progressively to a maximum of spironolactone, 400 mg/day, and furosemide, 160 mg/day

Complications of diuretic therapy 00:26:50

1. Acute kidney injury
2. Hepatic encephalopathy
3. Electrolyte abnormalities (hyponatremia)
   - Loop diuretics → hypokalemia
   - Spironolactone → Hyperkalemia
4. Painful gynecomastia (due to spironolactone)

Refractory ascites 00:31:36

- Inspite of maximum diuretic treatment / complication due to diuretic treatment

  10% cirrhosis patients → Refractory ascites

  Median survival → 6 months

  Management: 1) 1st line → Large volume paracentesis

  \+

  Plasma volume expansion

  Diuretics not given → 2) Exception: If adequate urine Na excretion present

  ↓

  To delay ascites formation

  Increase gap between large volume paracentesis

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TIPS 00:36:12

- Transjugular intrahepatic portosystemic shunt

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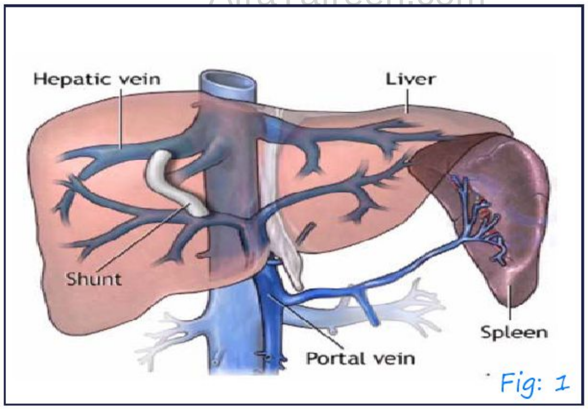

Fig: 1

- Shunt created between

  1.Intrahepatic branch of portal vein

  2.Outflow of hepatic vein

- Aim: To decompress the portal system
- Complication: Hepatic encephalopathy (when uncovered stent is used)

Other pharmacological agents 00:40:30

1.Midodrine

- α_1 adrenergic agonist
- oral
- vasoconstrictor

2.Clonidine

3.Vasopressin V2 receptor antagonist

4.Octreotide

5.Albumin

Alfa pump system 00:42:46

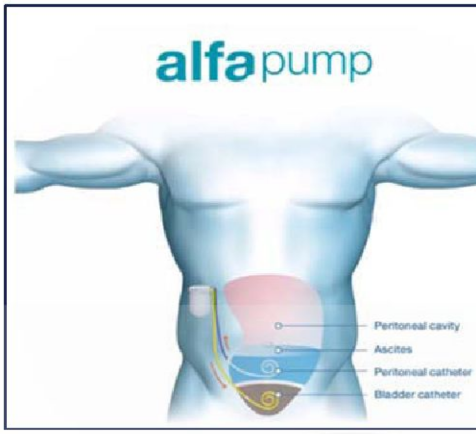

Fig: 2

- Automated pump which moves the ascites fluid from peritoneal cavity to urinary bladder
- Symptomatic treatment

Drug contraindications in ascites 00:44:28

1. NSAID's
   - ⊖ Renal prostaglandin synthesis
2. ACE Inhibitors / ARB's
3. Antibiotics
   (Aminoglycosides → Nephrotoxicity)
4. NSBB
   (Avoided in advanced cirrhosis).

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SPONTANEOUS BACTERIAL PERITONITIS

- Bacterial infection of ascitic fluid
- No other specific identifiable intra-abdominal cause

Pathogenesis of SBP 00:02:35

- Alternation of gut liver axis (Most important)
- Immune dysfunction
- Genetic factors: NOD2 gene

Alteration of gut liver axis

- Pathologic bacterial transduction
- Spillover of endotoxins in to systemic circulation

Clinical features of SBP 00:05:35

- Heterogenons in clinical presentation
- Asymptomatic
- Symptomatic

i. Abdominal pain/vomiting/diarrhea

ii. Fever/↑WBC/↑CRP serum

iii. Deterioration of LFT

iv. Hepato encephalopathy

v. AKI

vi. Septic shock

Diagnosis 00:08:18

- Neutrophil count in ascitic fluid (>250/mm^3 of ascitic fluid)
- Culture: Monomicrobial

Secondary bacterial peritonitis 00:09:55

- Polymicrobial infection

Treatment of SBP 00:10:40

- Empirical antibiotic therapy
- Risk of MDR bacteria
- Severity of infection
- Local epidemiology
- In case of community acquired SBP: Gram-ve organism
- Treatment:
- 3rd generation cephalosporin
- Fluoroquinolone
- Amoxicillin + Clavulanic acid
- In case of health care associated or nosocomial SBP

Low prevalence MDR	High prevalence of MDR
Rx: Piperacillin + Tazobactamm	Rx: meropenem +/- Vancomycin → MRSA/VSE Daptomycin/ linezolid→ VRE

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48hrs after starting antibiotics

↓

Repeat paracentesis

↓

(There should be fall in ANC by at least 25%) →

Recovering

Prophylaxis of SBP 00:18:18

- Selective intestinal decontamination by reducing gram negative bacteria
- Oral norfloxacin/Ciprofloxacin/Trimethoprim/Sulfamethoxazole

1° prophylaxis 00:20:48

- High risk individuals
- Primary: Norfloxacin, 400mg/day or ciprofloxacin 500mg/day or trimethoprim – Sulfamethoxazole, 1 Double strength tablet a day
- Criteria
- Cirrhosis with ascites
- Ascitic fluid protein <1.5g/DL
- Child pugh score ≥9 serum bilirubin level ≥3mg/DL serum creatinine level ≥1.2mg/dl and/or hyponatremia <130mEq/L

- Secondary: Norfloxacin, 400mg/day or trimethoprim-Sulfamethoxazole, 1 double-Strength tablet daily
- Criteria: All patients with a previous episode of SBP
- PT with in GI bleed → IV ceftriaxone 1g/day for 7days

2° prophylaxis 00:24:00

- After 1st episode of SBP
- 70% recurrence rate in 1st year
- Lifelong 2° prophylaxis required

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HEPATIC ENCEPHALOPATHY

- Spectrum of neurologic & Psychiatric manifestations
- Ranging from confusion → Coma
- Seen in
  i. CLD + Portal HTN
  ii. Acute liver failure
- Poor prognosis :
- 1yr survival rate → 42%
- 3yr survival rate → 23%

Pathophysiology 00:03:31

- Multifactorial
  i. Production of neurotoxins
  ii. Altered permeability of BBB
  iii. Abnormal synaptic neurotransmission
- Ammonia → Neurotin
- In 90% of pts with HE → Arterial hyperammonemia
- Ammonia synthesized in colon with in bacterial flora

Protein --Bacteria--> Ammonia → Enter portal circulation

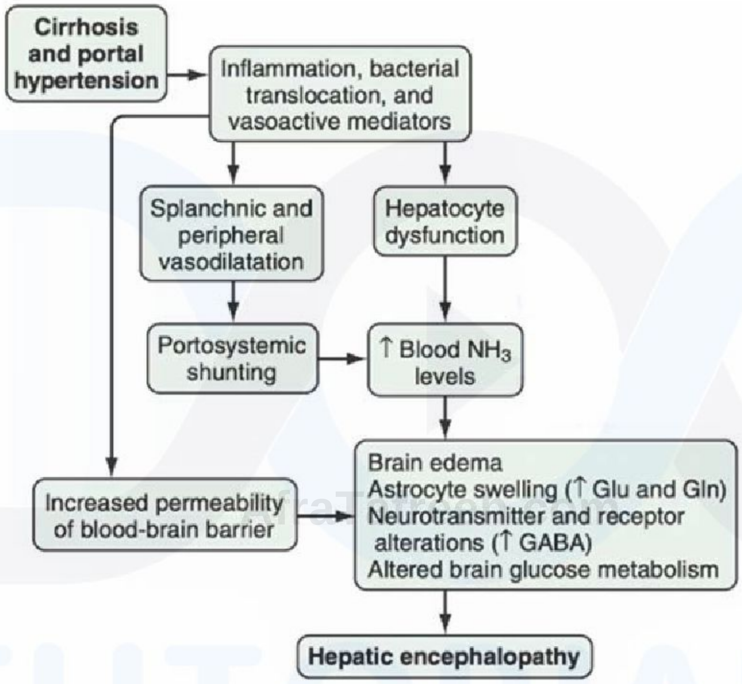
Enterocyte → Can synthesis ammonia from glutamine

Enter portal circulation → Cleared & Metabolized → Hepatocytes

- In cirrhosis → Hepatocyte dysfunction, Portosystemic shunting } Hyper ammonemia
- Impact of hyperammonaemia → Cerebral edema
  Astrocyte swelling
  Impaired transplant of myoinositol

Neurotransmitters involved in HE 00:10:24

- Activation of inhibitory system → GABA & Serotonin
- Inhibition of excitatony system → Glutamate /catecholamines
- End result → Neural inhibition



Clinical manifestations 00:13:19

- PT may have subtle manifestations & Reversal of sleep wake cycles
- Agitation
- Disinhibited behaviour
- Seizure
- Coma
- Flapping tremors
- Negative myoclonus

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- Asymmetric myoclonus
- Asterixis
- Constructional apraxia

Classification of Hepatic encephalopathy 00:17:10

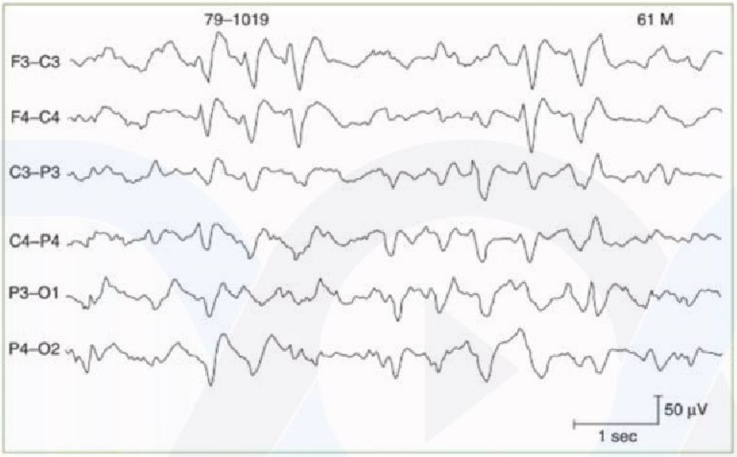
- Type A: HE associated with acute liver failure
- Type B: HE associated with portosystemic shunts in absence of Liver disease
- Type C: HE associated with CLD with portal hypertension (Most Common)

Precipitants of HE 00:20:25

- Alcohol
- GI bleed
- Constipation
- Diuretics
- Dehydration
- Electrolyte imbalance
- Infection

Diagnosis 00:21:50

- No specific lab finding
- Blood ammonia levels (Valproate can cause hyperammonemia)
- EEG – Triphasic waves



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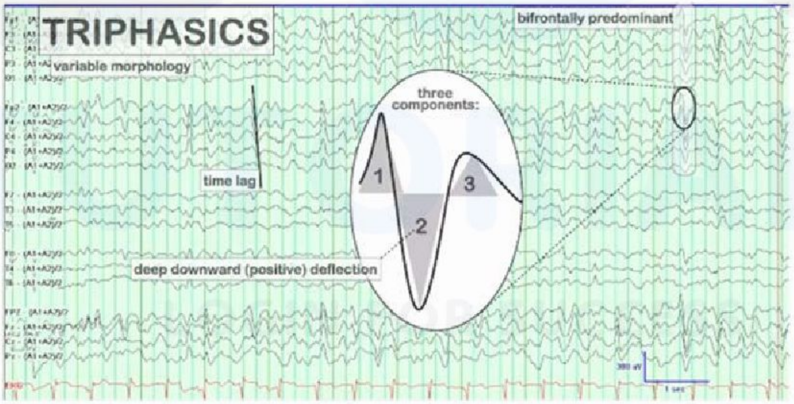

Treatment of HE 00:25:45

- Aim: Eliminate/correct precipitating factors

  i. Non absorbable disaccharide → Oral lactulose

  ↓

  Metabolised by gut bacteria

  ↓

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Byproducts reduce intestinal PH

↓

(↓) Ammonia absorption

Lactulose → 30-45ml orally 2-4times/day

↓

Given until pt passes 2-3soft stools/day

Can be given as enema

ii. Oral antibiotics (2nd line) → i. Modify intestinal flora
ii. Lower stool PH
iii. Enhance ammonia excretion

- Rifaximin → 550mg twice daily & 400mg thrice daily
- Neomycin

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iii. Branched chain amino acid supplementation

- LOLA
- L ornithine L Aspartate
- Acts by activating urea cycle → Enhance ammonia cleaning

iv. Zinc supplementation

- Mild benefit
- (↑) Activity of ornithine transcarboxylase
- Role of dietary protein restriction
- No significant role

HEPATORENAL SYNDROME

- Functional Renal failure due to severe hepatic injury
  (Most common
  Advanced cirrhosis)
- Reduction of kidney perfusion

Reduction in GFR 00:02:25

- 1.Renal vasoconstriction
- Progressive splanchnic vasodilation

↓

Reduction in effective arterial Blood volume

↓

RAAS activation

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HRS Forms 00:05:00

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- 2 Forms of HRS

i. Type 1 HRS
  - Acute form
  - Acute & rapid deterioration of renal function
  - Multiorgan failure

ii. Type 2 HRS
  - Chronic form
  - Insidious onset
  - Moderate Renal failure
  - Slowly progressive compared to type 1

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Type 1 HRS 00:07:08

- Acute decompensation in advanced cirrhosis
- Severe acute alcoholic hepatitis
- Subacute liver failure

Manifestation

- Rapidly progressive AKI
- Multiorgan Dysfunction
- Hepatic failure
- Adrenal in sufficiency

Precipitants

- Bacterial infection
- Gi Bleed
- LVP without albumin administration
- Rapidly progressive downhill course
- Death within 2-3 weeks if intreated

Type 2 HRS 00:11:00

- Liver cirrhosis + portal Hypertension
- Manifestation
  - Refractory ascites
  - Less severely jaundiced
- Slowly progressive course
- Mean survival time without treatment: 6 months

Main clinical characteristics of Type 1 and Type 2 Hepatorenal Syndrome

- Type 1 HRS
  - Acute and rapid deterioration in renal function (serum creatinine rise ≥ 2.5 mg/dl or 220 μmol/L in < 2 weeks)
  - Occurs in parallel with the failure of other organs or systems (e.g., coagulopathy, hepatic encephalopathy)
  - In cirrhosis, is a form of acute-on-chronic liver failure
  - Frequently follows a precipitating event, mainly bacterial infection
  - Rapidly fatal without treatment: Mean survival 2 to 3 weeks

- Type 2 HRS
  - Moderate stable renal impairment (average serum creatinine 2 mg/dl [176 μnol/l])
  - Mainly causes refractory ascites
  - Mean survival without treatment: 6 months

Treatment of HRS 00:13:26

- Ideal therapy: Improvement of liver function
- Pharmacotherapy → Reversal of AKI

  ↓

  - Vasoconstrictors + Albumin

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- Aim: to reverse splanchnic arterial vasodilation restoration of effective arterial blood volume
- Drugs: Terlipressin + Albumin
  Vasopressin + Albumin
  Norepinephrine + Albumin
  Midodrine + Octreotide + Albumin
- Vasopressin analogues → preferential Vasoconstriction
- Vasopressor → given for a max of 2 weeks
- Discontinue all hepatotoxic drugs
- Antibiotic indicated in case of infection

• TIPS
  - Diuretic resistant ascites
• Liver transplantation (Definitive T/t)

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VIROLOGY OF HEPATITIS B

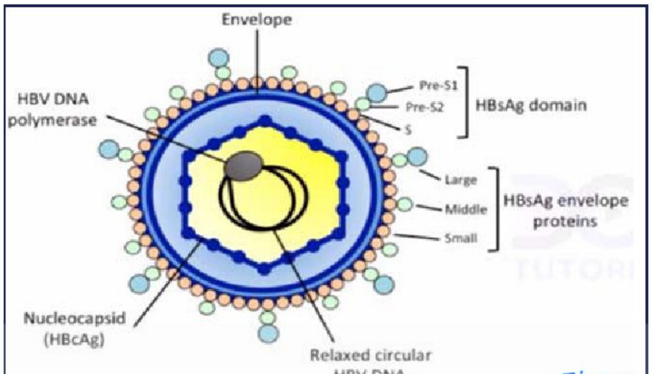

Fig: 1

- 42 nm small DNA virus
- DNA- genome
- Hepadna viridae family

  ↓ DNA

  Hepatotropic

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Viral Genome 00:03:48

- 2 linear strands of DNA

  ↓

  Held in a circular configuration
- Strands – Complete strand /minus strand
  – Incomplete strand/plus strand
- DNA → Partially double stranded
  → Partially single stranded
- Viral DNA polymerase a/w plus strand
- 4 overlapping genes'
  - S gene
  - C gene

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- P gene
- X gene

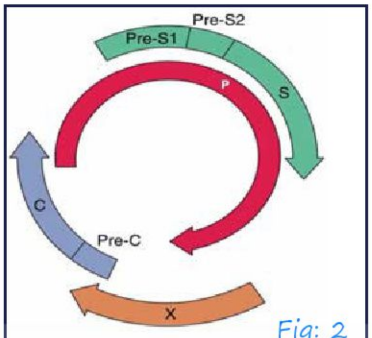

Fig: 2

S gene 00:07:28

- S region & 2 Pre-S regions { Pre S1 region / Pre S2 region
- S region codes for major envelope portion → HBsAg

↓

Aka

↓

Australia antigen

- Translation starting form Pre S2 region → M protein /Middle portion
- Translation starting from Pre S1 region → L protein/large protein

↓

Present only in "complete virion"

- M protein & S protein → also present in HBsAg particles

Antigenic Diversity of HBsAg 00:11:51

- 2 antigenic components
  - Common group reactive antigen "a" → Common to all HBsAg isolates
  - 2 pairs of subtype specific antigens → d-y, w-r
- 4 major antigenic subtypes:
  - adw
  - adr
  - ayw
  - ayr
- 10 genotypes (A-J)
- A & D → US& Europe
- B& C → Asia
- Genotypes B → less rapid progression (in compression to other)

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C gene 00:17:35

- C gen codes for:
  - C antigen
  - E antigen
- 2 regions
  - C region (core)
  - Pre-C region (Pre core)
- C region translation → HBcAg (core Antigen)
- Pre-C region translation → HBeAg

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HBcAg Vs HBeAg 00:19:48

HBcAg	HbeAg
No signal peptide	Has signal peptide
Not secreted into circulation	Secreted into circulation
Assembles into nucleocapsid	
Demonstrated via immunofluorescence inside hepatocytes	Marker of HBV replication & infectivity
Anti HBcAb → appears in Blood	

- HbeAg positive mothers → 90% transmission to offspring
- HbeAg negative mothers --> 10-15 % transmission to offspring
- HbeAg → appears transiently
    - → disappears later
      ↓
      Sign of Recovery
    - → If persistent beyond 3 months
      ↓
      Sign of chronic progression
- Chronic Hep B: i. ongoing viral replication
    ii. High infectivity
    iii. Inflammatory liver injury

X gene 00:27:00

- Codes for HBx
- HBx have Transactivating effects

↓

Increase rate of transcription

↓

Enhanced replication of HBV

- HBx releases Ca+2 from mitochondria

↓

Affects signal transductions pathways

↓

Trans activating effects

- Role in carcinogenesis → Inactivates P53 gene

P gene 00:29:52

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- Codes for DNA polymerase enzyme
- Important for replication & Repair of HBV DBA
- Largest of all 4 gens
- 2 activities
  - DNA dependent DNA polymerase
  - RNA dependent Reverse Transcriptase

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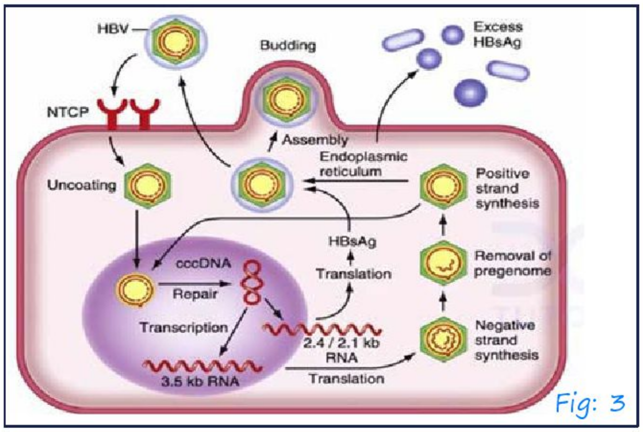

Fig: 3

- From a pre-genomic RNA intermediate → Minus strand originates
- Hepatitis B virus → replicates like Retrovirus
- Serum of patent with Hepatitis B

  i. Complete Hepatitis B

  - Dane particle
  - 42 nm

  ii. Spherical particles (most abundant)

  - 22nm

  iii. Filamentous particles

  - 22 nm
- Ratio of spheres & filaments to complete virions = 100-1000

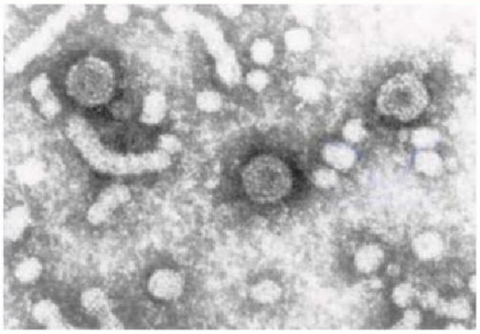

Fig: 4

Mutations in HBV genome 00:39:02

i. Pre core mutation

- Complete absence of HbeAg production
- Nucleotide 1896 position → absence of HbeAg position

ii. Basal core promoter mutation

- Reduction in HbeAg (70%)
- Nucleotide 1762 & 1764 position

iii. i &ii → Loss of Immune tolerizing effects of HbeAg

→ Increase risk of HVV

iv. Escape mutant

- Mutation in common A determinant of HBsAg
- Not neutralized by anti HBs
- Challenge in hepatitis B prophylaxis

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Transmission of Hepatitis B virus 00:44:30

- Blood Borne virus
- Percutaneous /mucus membrane exposure
- Mode: - Parenteral
  - Sexual
  - Perinatal
  - (Infected body fluids)
- HBV is - 50- 100 times as infections as HIV
  - 10 times as infections as HCV
- Needle stick injury: - HBV→ 30 %
  - HCV → 3 %
  - HIV → 0.3 %

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Carrier of HBV 00:49:27

- HBsAg > 6 months
- Only – 5-10 % adults
  - 30 % children
  - 90% neonates

Super carrier

- Highly infection's
- Increase HBsAg + HbeAg + increase polymerases + increase Transaminases

Simple carrier

- Low infections
- Low HBsAg; HbeAg-; No DNA polymerases

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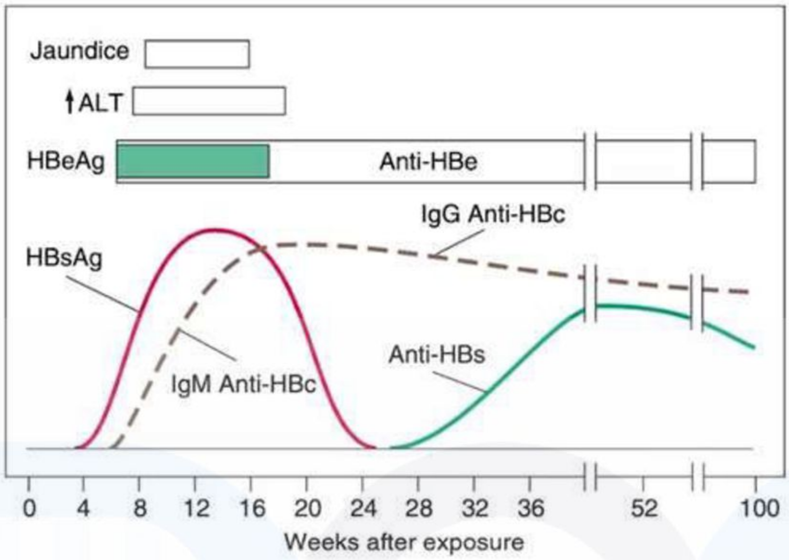
SEROLOGICAL AND VIROLOGICAL MARKERS OF HBV



HBsAg 00:00:55

- HBsAg
  - First detectable Biomarker
  - 1-12 Weeks of exposures
    ↓
  - Becomes undetectable after 1-2 months of jaundice
  - If persistence > 6 months: chronic infection of HBV
  - Levels of HBsAg not proportional to severity

HBcAg 00:04:20

- HBcAg → not detectable in serum
- Anti HBc → Detectable in serum
  → 1-2 weeks oater HBsAg

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Window period

- Period between – disappearance of HBsAg & Appearance of anti BBs
- Anti HBc Ab is only detectable

In acute	In chronic
Anti HBc IgM	Anti HBc IbG

False +ve IgM anti HBc

- High titer of RA factor

Chronic hepatitis B

- Reactivation → Re-expression of anti HBc Ab IgM

Hepatitis B vaccine

- Anti HBs Ab
  ↓
  Protective Ab
  ↓
  a/w resolution of HBV infection

HbeAg 00:15:42

- Concurrently or shortly after HBsAg
- Definite correlation with viral replication /detectible HBV DNA levels

Self-limited HBV infection

- HbeAg
- Anti HBeAb → lower infectivity

In choric HBV

HBsAg   IgG Anti HBc Ab

> 6 m

In early chronic HBV

HBV   DNA

Serum   Hepatocyte nuclei

- Highly replicative sate
- Time of maximal infectivity& liver injury
- HBV DNA → quantitative marker of replicative phase
- HBeAg → qualitative maker of replicative phase

Non replicative phase

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- Seroconversion

HbeAg   Anti HBeAb

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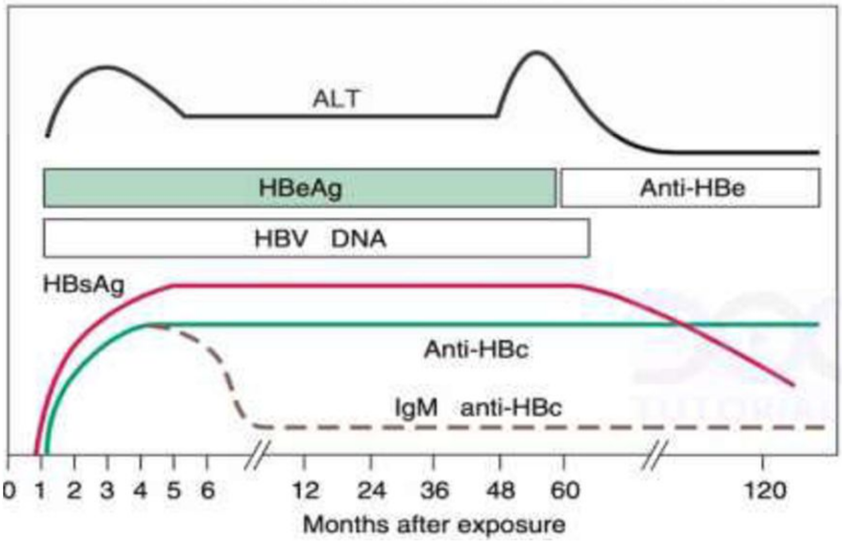

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- Cell mediated immune clearance of virus infected hepatocytes
- HBV DNA → found in hepatocyte nuclei only
  → Integrated into Host genome
- Inactive HBV Carriers:
- Sometimes non replicative phase can turn into replicative phase
- Re expression of HBeAg and HBV DNA
- IgM Anti HBe Ag
- Causes liver injury

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CLINICAL COURSE AND MANIFESTATION OF HEPATITIS

Acute phase	Chronic phase
Subinical – Anicteric Hepatitis to icleric hepatitis Rarely: Fulminant hepatitis (0.1-0.5%)	Asymptomatic carries to chronic hepatitis/Cirrhosis/HCC
Both can have extra hepatic manifestations	

Acute hepatitis B 00:03:32

- Incubation period: Few weeks – 6months (Avg: 60-90days)
- Asymptomatic (Mostly)
- Especially in children
- Symptomatic
- Nausea/Vomiting
- Fever/Arthralgia/Rash

(d/t immune complexes → HBsAg – anti Hbs immune complexes)

↓

Deposited in synorium/Cutaneous blood vessels

↓

- Jaundice (In 30% patients)
- ↑ Level of transaminases (ALT > AST)
- Best marker of prognosis: PT-INR

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- Symptoms disappear in 1-3months
- Best viral biomarker: IgM anti HBc Ab
- HBsAg > 6 months
- Chronic hepatitis B
- Severe liver disease
- Individual laving: Underlying liver disease & Other hepatic viral infection

Fulminant hepatitis 00:13:20

- Massive immune mediated lysis of infected hepatocytes
- Multiorgan dysfunction
- Hepatic encephalopathy

	Acute viral hepatitis (AVH-B)	Acute liver failure (ALF-B)
Prodromal symptoms	Present	
Sudden jaundice	Present	
AST/ALT	Markedly elevated	
IgM anti-HBC	Positive	
Encephalopathy	Absent	Present
Coagulation	Near normal	Markedly deranged
Liver size	Slightly large	Small

Chronic hepatitis B 00:15:46

- Asymptomatic carrier → Cirrhosis/HCC
- May or may not have associated with symptomatic hepatitis
- Asymptomatic/Fatigue → Decompensated stage

- Jaundice
- Hepatic failure
- Hypersplenism
- Hypo albuminemia

→ Icterus
→ Ascites
→ Edema
→ HSM

Natural history of chronic hepatitis B

Chronic hepatitis B

Immune tolerant phase	Immune active phase	Immune control phase	Immune clearance (cure) ↓ Reactivation phase

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Differences in different phases

- Serum ALT levels
- HBeAg status
- Viral load

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Immune tolerant phase 00:23:00

- Weak host immunity against HBV
- Viral load → High
- ALT/AST levels – Low
- No/Minimal attack on infected hepatocytes

Immune active phase 00:25:30

- Host immunity becomes stronger
- Infected hepatocytes are attacked
- ALT/AST levels: High
- Viral load: Decreases

Immune control phase 00:27:14

- Host immunity becomes stringer
- ↓ Viral load

Immune clearance phase 00:28:08

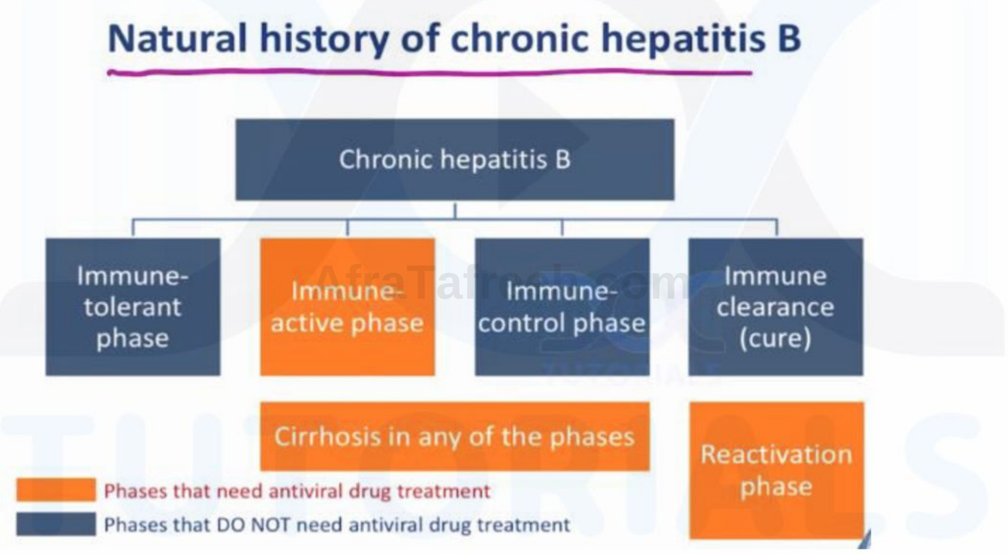
- HBeAg negative phase
- HBsAg negative
- Anti HBcAb (+)
- (N) AST/ALT levels
- Almost undetectable serum HBV levels

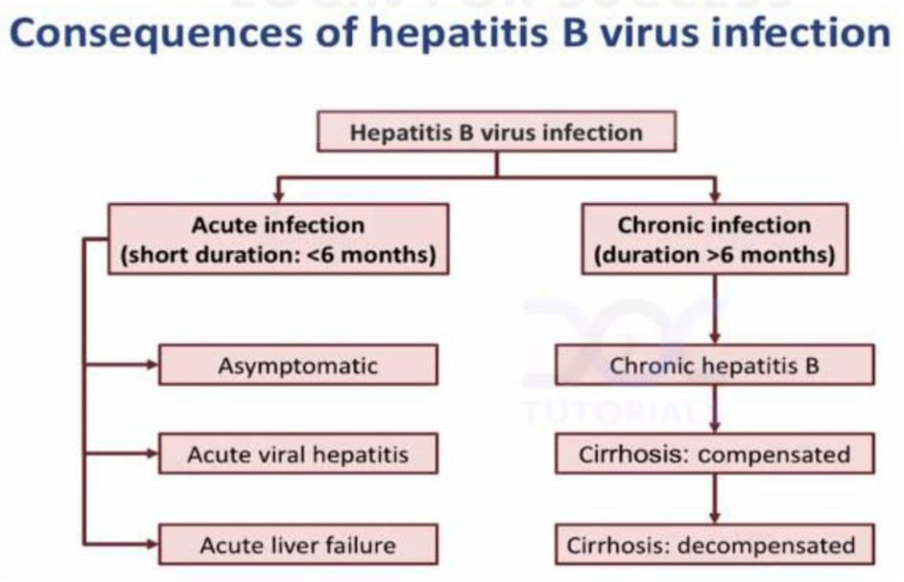
Reactivation phase

- Whenever host immunity falls
- (↑) viral load
- HBV DNA (+)
- (↑) ALT/AST levels
- HBeAg seroconversion
- About 30% of pt HBeAg seroconversion → Active disease

↓

Preferential selection of
HBeAg negative mutants
Pre cone mutations
Core promotes mutations





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Extra hepatic manifestations 00:34:40

- Occurs d/t aberrant immunologic response to the extrahepatic viral proteins
- May even occur without clinically apparent liver disease
- Serum complements levels: Low
- Role of anti-viral therapy: Significant → Reduce immunologically active viral antigens

Clinical features

- Arthritis/Dermatitis
- PAN
- Glomerulo nephritis
- Cryoglobulinemia

Arthritis/Dermatitis

- Differential diagnosis: Inflammatory arthritis

PAN

- 30% of PAN; Infected with in HBV
- Chronic Hep B: <1% PAN

Glomerulonephritis

- Membranous glomerulonephritis
- MPGN

Cryoglobulinemia

- Type II/III cryoglobulinemia → Associated with hepatitis B

Type II	Type III
Poly cloral IgG & monoclonal IgM	Polycloral IgG & monoclonal IgM

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TREATMENT OF HEPATITIS B

- AASLD – American association study of liver diseases (2018)
- EASL – European association for study of liver
- APASL – Asian pacific association for study of liver

Acute hepatitis B 00:04:48

- Symptomatic acute hepatis B
- Antiviral therapy; Not necessary generally
- >95% pts immune competent → Recover spontaneously
- Indications for anti-viral in acute hepatitis B
- Protracted – Severe hepatitis B
  - i. >4weeks
  - ii. PTINR >1.5
  - iii. T. Bilirubin >3mg%
  - iv. D. Bilirubin >1.5mg%
- Drugs
  - ENTECAVIR
  - TENOFOVIR

  (ENTECAVIR, TENOFOVIR) Till HBsAg clearance in liver transplant: Indefinitely
- IFN - α → Not given/Contraindicated in acute hepatitis B
- HBsAg >6months → Chronic hepatitis B

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Chronic hepatitis B 00:11:30

- When to treat with in antivirals
  i. High serum HBC DNA levels
  ii. Elevated serum ALT levels
  iii. Advanced hepatic Fibrosis/Cirrhosis
  iv. HBeAg status
  v. HBV genotype
  vi. Age
  vii. Comorbidities

HBV DNA

- (↑) Levels of HBV DNA (Poor prognosis)
  i. High risk for cirrhosis
  ii. High risk for HCC
  iii. High risk for liver disease related morbidity & mortality
- Inactive chronic Hep B: HBV DNA levels <2000 IU/ML
- Immune active chronic Hep B: HBV DNA levels >20,000 IU/ML
- HBeAg neg CHB < HBeAg CHB → HBV DNA levels

ALT levels

- Association with outcome but not as strong as HBV DNA
- Therefore, known as imperfect marker

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- Liver fibrosis
- Assessed with Non-invasive/Invasive methods

Non-invasive:

i. Ultrasound elastography
   - Liver stiffness

ii. Serum based fibrosis markers
   - Fibrosure
   - FIB-4
   - APRI
   - ELF

Invasive:

i. Biopsy

Antivirals 00:24:50

- Peg IFN alpha (Interferons)
- Nucleotide/Nucleoside analogues coral

i. ENTECAVIR

ii. TENOFOVIR

iii. LAMIVUDINE

iv. ADEFEVIR

v. TELBIVUDINE

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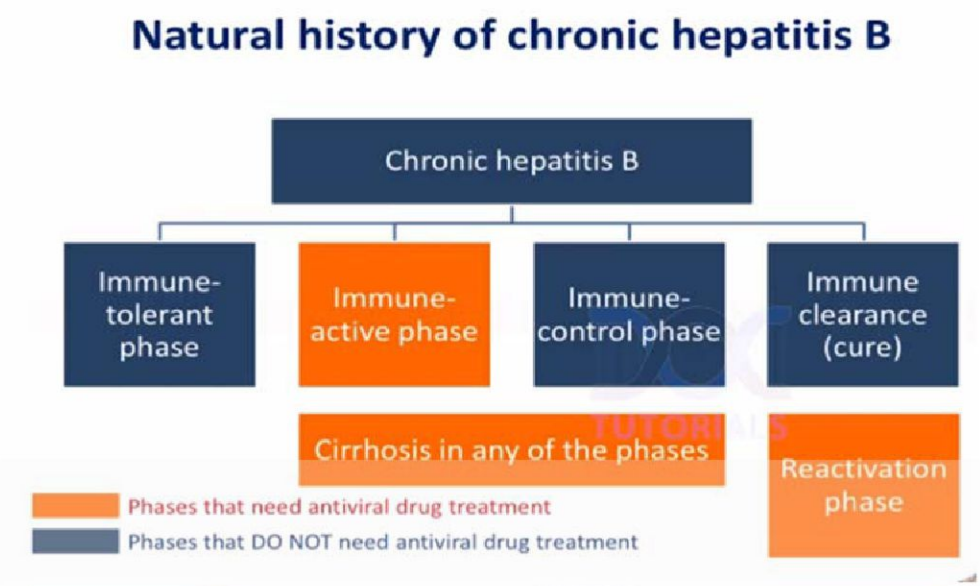

- Lamivudine → 1st drug approved for use
- Disadvantage: Rapid development of mutations in YMDD active site of DNA polymerase
- Entecavir/TDF/TAF → Good outcome

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Immune active phase 00:33:20

- ALT > 2 upper limit of normal
  - Males → 35 U/Lit
  - Females → 25 U/Lit
- HBV DNA (↑) (↑)
  - HBeAg (+) → > 20,000 IU/ml
  - HBeAg (-) → >2,000 IU/ml
- Significant histologic disease
  - Drugs used: Entecavir, Tenofovir, peg IFN alpha

Immune active CHB with cirrhosis

- Antiviral therapy

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- If HBV DNA > 2000 IU/ML
- Regardless of ALT levels

Immune tolerant CHB

- No need of antiviral treatment
- ALT levels monitored every 6months

HBeAg (+) immune active CHB

↓

Undergone treatment

↓

Achieved seroconversion

↓

Consolidation therapy

Normal valves of ALT & Undetectable HBV DNA for at least 12months

↓ After 12months

Monitored every 3months

If recurrent viremia

ALT Flares

Clinical decompensation

HBeAg (+) Immune active CHB + Cirrhosis

↓

Undergone treatment

↓

Achieved seroconversion

↓

Indefinite antiviral therapy

HBeAg (-) Immune active CHB

↓

Indefinite antiviral treatment

Presence of precore mutant

HBeAg has immunomodulatory properties

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POST EXPOSURE PROPHYLAXIS OF HEPATITIS B

Unvaccinated individual 00:01:02

- Unvaccinated individual
- 1.HB IG (0.06ml/kg)
- In less than 7days
- 2.Hepatitis B vaccine (0, 1, 6months)

Vaccinated individual 00:02:20

Responder	Non responder
Anti HBs Ab titre	Anti HBsAb titre
>10 mIU/mL	<10mIU/ml
↓	↓
No further action required	i. HBIG (0.06m/1kg) ii. Hepatitis B vaccine 2 series of vaccination → 2doses HBIG (1month apart)